Immunoadsorption Followed by Rituximab as a Definitive Treatment for Insulin Autoimmune Syndrome (Hirata Syndrome): A Case Report

Tim M. Kroemer,[1] Anne Erler,[2] Elena Tsourdi,[1] Matthias Gruber,[1] Sergey Tselmin,[3] Ulrich Julius,[3] Martin Aringer,[2] Lorenz C. Hofbauer,[1] and Tilman D. Rachner[1]

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A 59-year-old Caucasian man (170 cm, 78 kg, BMI 27 kg/m^2) was referred for evaluation of recurrent episodes of severe hypoglycemia, which had commenced a week earlier. Computed tomography and MRI scans excluding abnormalities of the pancreas had already been performed. The patient had previously suffered from arterial hypertension, hyperlipoproteinemia, and an acute myocardial infarction the year before. Pharmacological therapy consisted of a β-receptor antagonist, a statin, low dose aspirin, clopidogrel, and vitamin D. Importantly, there was no history of alcohol abuse or diabetes and no previous exposure to antidiabetes medication (Fig. 1). Upon admission, the patient showed a sustained need for intravenous glucose supplementation with repetitive symptomatic declines of blood glucose to levels of relevant hypoglycemia (<2.5 mmol/L) immediately after discontinuation of parenteral glucose.

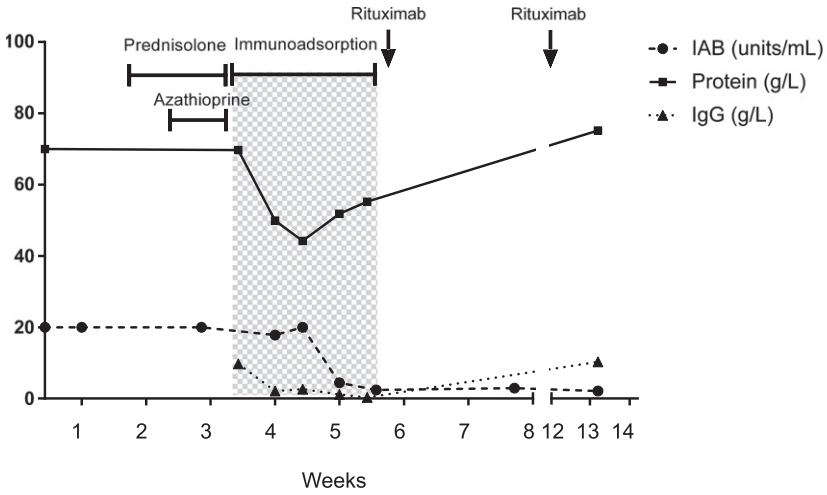

Figure 1—Serum parameters in relation to the course of treatment. Results of IAB, protein, and IgG are depicted in the graph during the weeks the patient was treated. The shaded area between weeks 3 and 6 represents the period when immunoadsorption was performed.

Further studies were performed under the assumption of an autonomous insulin secretion, as high serum levels of insulin (2.2 nmol/L; normal range 0.02–0.12 nmol/L) and C-peptide (2.23 nmol/L; normal range <0.26–1.39 nmol/L) during hypoglycemia had been documented. An endoscopic ultrasound of the pancreas showed no suspicious lesions, and a somatostatin receptor positron emission tomography/computed tomography scan showed no signs of an extrapancreatic insulin-producing tumor. Following the exclusion of an insulinoma, we considered rarer causes. Immunological testing by ELISA (MEDIPAN, Berlin, Germany) revealed highly positive anti-insulin antibodies (IAB) (>20 units/L; normal range <2.4 units/L). This, in combination with the elevated insulin levels and severe hypoglycemia established the diagnosis of an insulin autoimmune syndrome (IAS) (Hirata syndrome) as the underlying cause. Hirata syndrome is a rare condition in which autoantibodies against insulin decrease degradation of insulin, resulting in fasting hypoglycemia and elevated serum insulin levels. The etiology of IAS is not fully understood. Suggested triggers include certain HLA class II types (1) and exposure to drugs containing sulfhydryl groups or lipoic acids (2). No established treatment

[1]*Division of Endocrinology, Diabetes, and Bone Diseases, Department of Medicine III, and Center for Healthy Aging, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany*
[2]*Division of Rheumatology, Department of Medicine III, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany*
[3]*Lipidology and Lipoprotein Apheresis Center, Department of Medicine III, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany*

Corresponding author: Tilman D. Rachner, tilman.rachner@uniklinikum-dresden.de.

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protocols exist. An initial treatment approach with prednisolone (40 mg/day) for 13 days had no impact on the hypoglycemia, and immunosuppression with azathioprine (50 mg/day) was attempted. After another week with continuous need for intravenous glucose supplementation, the patient was offered immunoadsorption in an attempt to reduce the circulating IAB. Hence, 10 daily sessions of immunoadsorption using a reusable adsorber system loaded with sheep antigens directed against human immunoglobulin were performed. Remarkably, within four sessions, glucose supplementation could be withdrawn. While we cannot exclude a spontaneous remission, which has been described in other cases, IAB steadily declined during treatment, returning to the lower limit of detection after the tenth session (Fig. 1). Successful treatment of IAS by administration of rituximab has been reported (3). Although immunoadsorption sufficiently reduced IAS in our patient, we chose to sequentially administer two doses of 1 g of rituximab in an attempt to reduce the risk of relapse. Following an unremarkable 5-h glucose tolerance test after the first administration of rituximab, the patient was discharged from the hospital. No new episodes of hypoglycemia were reported when the patient returned for the second dose of rituximab 14 days later. The level of IAB had remained unremarkable, whereas serum protein and IgG levels had normalized again (Fig. 1). Currently, no recurrence of disease has been documented for more than 12 months to date, indicating a sustained response to our therapeutic approach. To our knowledge, this is the first reported sequential therapy of immunoadsorption followed by rituximab for the treatment of Hirata syndrome. This treatment either combined or alone requires prospective evaluation.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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