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Antibody-Mediated Insulin Resistance: When Insulin and Insulin Receptor Act as Autoantigens in Humans

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ABSTRACT

We report the case of a patient with diabetes presenting a severe insulin-resistance syndrome due to the production of insulin autoantibodies by a lymphocytic lymphoma. We describe the various mechanisms leading to the production of insulin autoantibodies and insulin receptor autoantibodies and review the therapeutic possibilities.

Mots clés :
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RÉSUMÉ

Nous rapportons le cas d'un patient diabétique présentant un syndrome d'insulinorésistance grave dû à la production d'auto-anticorps anti-insuline par un lymphome lymphocytique. Nous décrivons les divers mécanismes menant à la production d'auto-anticorps anti-insuline et d'auto-anticorps anti-récepteurs de l'insuline, et passons en revue les possibilités thérapeutiques.

Introduction

Autoimmune diseases are relatively common and include well-known diseases such as type 1 diabetes. The immune system is adapted to identify and eliminate foreign antigens and the organisms bearing them. When there is a failure in the immunologic control mechanisms that maintain self-tolerance, the adaptive immune system can be directed at a self-antigen. In most cases, the autoantigen continues to be produced and, thus, cannot be eliminated by the immune response. In these cases, the adaptive immune response becomes chronic, resulting in disruption of normal physiologic functions. Autoimmune diseases can be categorized as humoural or cellular, depending on whether the disease pathology is dependent largely on autoantibodies (e.g. systemic lupus erythematosus) or cytotoxic T cells (e.g. type 1 diabetes). Whereas autoimmunity in diabetes usually matches with type 1 diabetes, practitioners should be aware of rare cases of diabetes due to antibody-mediated severe insulin resistance. Such a clinical condition normally involves the presence of autoantibodies directed against endogenous insulin and/or to the cell-surface insulin receptor. Such autoantibodies deeply alter tissue insulin action, leading to inefficacy of endogenous or exogenous insulin to maintain glycemia within the normal range.

Case Report

We report the case of an 83-year-old male patient who was diagnosed with diabetes at the age of 72. This patient was referred to the endocrinology department for an acute ketoacidosis with an extreme insulin resistance syndrome 10 years after the diagnosis of diabetes. Concerning his medical history, he was being treated for ischemic cardiomyopathy, peripheral arterial disease and high blood pressure and was being followed for an autoimmune thrombocytopenia. In terms of diabetes, he presented with optimal blood glucose control, with glycated hemoglobin (A1C) levels at 7% under oral antidiabetic drugs until the start of insulin therapy 3 years before his hospitalization in our department. At the initiation of insulin, the A1C level was at 9.9% but rapidly decreased to 7% with fewer than 80 units of insulin per day (1.6 IU/kg/day). He developed

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gradually, in 1 year, a deterioration of blood glucose control with A1C levels between 11% and 12% and multiple hospitalizations for acute ketoacidosis and severe insulin resistance. In our department, insulin requirements in a syringe pump were provided at up to 100 units per hour. Despite high insulin levels, he presented with several episodes of acute ketoacidosis, with blood ketone levels of up to 5.9 mmol/L and a pH level of 7.31.

Based on the diagnosis, the cause of his diabetes was unclear; no argument was present for type 1 or 2 diabetes or secondary diabetes. Indeed, he was never overweight, and there were no cases of diabetes in his family. The imaging of the pancreas was normal, and the tests for endocrinopathy (low-dose dexamethasone suppression test, thyroid stimulating hormone, growth hormone, insulin-like growth factor-1), hemochromatosis and type 1 diabetes antibodies came back negative. He did not develop acanthosis nigricans. Serum C-peptide levels were measurable at 1 mmol/L. The anti-insulin antibodies were positive at a high titre of 92% (including 91.8% of free antibodies). The anti-insulin antibodies were measured by radioimmunoassay (RIA Cisbio Bioassays, Codolet, France) with iodine-125 radiolabeled insulin. The anti-insulin receptor antibodies were negative.

In parallel with this extreme insulin resistance, a lymphocytic lymphoma was diagnosed with monoclonal immunoglobulin M. The therapeutic management of this lymphoma by chemotherapy, including cyclophosphamide, rituximab and corticosteroids, resulted in an improvement in glycemic control (A1C levels at 7.8% at 1 month and at 1 year after chemotherapy), a decrease in insulin needs (after the second cure of chemotherapy, the insulin needs decreased to an average of 50 units per day until 1 year after the treatment) and anti-insulin antibodies levels (above 90% initially and then at 62.1% at 1 month after the end of the chemotherapy). Concerning the lymphoma, the treatment allowed a remission for several months with a disappearance of the peak monoclonal IgM and regression of lymph nodes. Unfortunately, 14 months after the end of chemotherapy, the patient presented with a lymphoma recurrence associated with an increase in anti-insulin antibodies and a recurrence of the severe insulin resistance (insulin requirements up to 400 units per day). A new chemotherapy was delivered, permitting 1 more time, an improvement in glycemic control. So, in this case, a close relationship had been established between anti-insulin antibodies, severe insulin resistance and lymphocytic lymphoma.

Discussion

In this case report, tumourous autoantibodies directed against insulin were responsible for severe insulin resistance that led to ketoacidosis. The presence of circulating autoantibodies directed against insulin can be found in 2 situations: in patients treated with exogenous insulin and in insulin-naive subjects.

Autoantibodies directed against insulin

The appearance of autoantibodies directed against exogenous insulin was demonstrated for the first time in 1956 by Berson (1). The first injection of insulin, extracted from porcine pancreas, in humans was performed in 1922 on a young Canadian, Leonard Thompson, who had had diabetes for 14 years. From 1923, laboratories began to produce insulin extracted from the pancreases of cows and pigs. This first exogenous insulin included other highly immunogenic molecules such as the pancreatic polypeptides proinsulin and C-peptide. At that time, the prevalence of autoantibodies directed against insulin was very high, greater than 95% (2). In 1970, porcine insulin began to be purified, and in 1978, a human form of insulin was developed by genetic engineering. Since the use of recombinant human insulin or highly purified insulin analogues began, the prevalence of autoantibodies directed against insulin has decreased, but it is still a common condition. Indeed, the conformational or structural modifications from the native form of insulin of currently available human insulin analogues can induce immunogenic responses. The mode of insulin administration could influence the development of antibodies directed against exogenous insulin. Indeed, the continuous intraperitoneal administration by insulin pumps increases the risk for development of anti-insulin antibodies in some patients with diabetes (3). Some genetic factors of susceptibility have been identified for the development of autoantibodies directed against insulin. Indeed, the HLA genotype would play a role in presenting insulin peptides to T cells (4). The HLA-DR7 subtype is associated with a higher rate of insulin autoantibodies, whereas being homozygous for HLA-B8, DR3 and C4AQ0 could be protective (5,6). In most cases, insulin autoantibodies are polyclonal IgG with a kappa light chain and lambda variables associated with 2 types of binding to insulin: high affinity/low capacity or low affinity/high capacity. Although insulin antibodies reportedly exist in about half of patients with type 2 diabetes who inject insulin, these antibodies do not often affect blood glucose levels severely. However, in insulin-treated subjects, insulin autoantibodies generally have low binding capacities and high binding affinities for insulin that may be responsible for insulin resistance (7). Greenfield et al (8) described the case of a 68-year-old woman with type 2 diabetes treated by insulin, who presented a major loss of glycemic control associated with severe insulin resistance induced by insulin autoantibodies. The woman had an HLA DR7 genotype, and insulin autoantibodies were polyclonal IgG. Likewise, Segal et al (9) reported the case of a young patient with diabetes evolving for 5 months who developed severe insulin resistance due to endogenous production of IgG against insulin. Less often, insulin-treated subjects develop insulin autoantibodies with very low binding affinities but high binding capacities for insulin. Thus, Tsuneo Ishizuka et al (7) reported the cases of 2 subjects with long durations of diabetes who developed insulin autoantibodies after the replacement of regular human insulin by human insulin analogues. They presented with severe hyperglycemia all day long and hypoglycemia in the mornings. The analysis of insulin autoantibodies demonstrated a very low binding affinity but a very strong binding capacity for insulin.

In insulin-naive subjects, insulin autoantibodies lead to a transient postprandial state of insulin resistance followed by hypoglycemia. This is due to the low binding affinity but the high binding capacity of autoantibodies for insulin. Such a condition is seen in the autoimmune hypoglycemia syndrome (Hirata syndrome), a rare condition first described in 1970. In non-Asian people, the Hirata syndrome is often associated with systemic lupus erythematosus or rheumatoid arthritis (4). It is characterized by a state of postprandial hyperglycemia when insulin is bound to the antibody and by late postprandial or fasting hypoglycemia when insulin is detached from the antibody. Antibody-induced insulin resistance can also be seen in hematologic malignancies and solid cancers. In 1981, Rhie et al (10) reported 2 cases of patients with diabetes with severe insulin resistance associated with monoclonal gammopathy (Waldenström macroglobulinemia and multiple myeloma with IgA gammopathy). It was suggested that the severity of insulin resistance was due to the production of an immunoglobulin with anti-insulin activity. On the other side, hypoglycemias induced by autoantibodies directed against insulin that linked insulin with low affinity have been reported in myeloma (11–13). Concerning solid cancers, Mizuhashi et al (14) reported the case of a 62-year-old man with insulin-treated type 2 diabetes associated with lung cancer. This patient developed several immunologic reactions against insulin and severe insulin resistance syndrome. His serum insulin level was elevated (912 pmol/L while fasting) due to high levels of IgG anti-insulin antibodies (99.7% bound) (14). This patient presented an immediate allergic reaction by producing IgE directed against insulin,