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Case Report

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Induction of Insulin Antibodies and Insulin Allergy under Alpha-Interferon Treatment of Renal Cell Carcinoma in a Patient with Insulin-Treated Diabetes mellitus – A Case Report

Key Words

Insulin allergy
Insulin antibodies
 α -Interferon treatment
Diabetes mellitus
Side effects of α -interferon treatment
Human insulin

Abstract

The induction of insulin antibodies and the development of an insulin allergy were observed in a male diabetic patient treated with insulin during α -IFN therapy of renal cell carcinoma. Diabetes and renal cell carcinoma were diagnosed at the same time. The patient was treated with biosynthetic human insulin and nephrectomy was performed. Four months later, antineoplastic chemotherapy was started (α -IFN, vinblastin). Six weeks after initiation of α -IFN injections, the patient reported signs of insulin allergy. Significant titers of insulin antibodies of both the IgG and IgE subclasses were found in the serum at that time and during follow-up, but not before the treatment with α -IFN. None of the other autoantibodies investigated were positive.

Introduction

It is well known that treatment with α -IFN induces autoimmune reactions. Autoantibodies against thyroid, nuclear antigens, liver antigens, red blood cells and other tissues were reported by several investigators [1–10].

The induction of an immune response against human insulin under α -IFN treatment has not been reported previously.

Case Report

The patient (male, 38 years old, body weight 60 kg, BMI 20.8 kg/m²) was admitted to our hospital with newly diagnosed diabetes mellitus. It was difficult to classify the diabetes type. The patient's age, the presence of ketonuria, the insulin requirement and the low values of basal and stimulated insulin and C-peptide secretion (data not shown) were indicative of insulinopenic diabetes. However, islet cell antibodies,

glutamic acid decarboxylase antibodies and insulin (auto)antibodies were not detectable.

The HLA type is HLA-A 3,23; B 44,18; Cw 4,7; Bw 4,6; DR 13 (6),7; DRw 52,53; DQw 6(1),2.

The patient had a history of alcohol abuse (100 g/day).

He was treated with human insulin from the very beginning (initially, Huminsulin Normal®, Lilly, 4 × per day – 70 U/day = 1.17 U/kg BW, later together with Huminsulin Basal®, Lilly, in a conventional intensified insulin therapy).

During routine investigations carried out on admission a tumor of the right kidney with a diameter of 4 cm was diagnosed by sonography and later confirmed by intravenous urography and computer tomography. The patient was transferred to the Department of Urology, St. Georg Municipal Hospital, Leipzig. A nephrectomy was performed. The report from the Department of Pathology gave the following histology: renal cell carcinoma, diameter 5 cm, numerous tumor invasions (penetrations) into the renal veins, tumor stage G₁, pT_{3b}. Antineoplastic chemotherapy was recommended. Insulin therapy was not interrupted.

Four months later, therapy with recombinant α -IFN (IFN α 2b, Intron®) and vinblastin was started. The patient received 21 injections of

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5×10⁶ units Intron® (3 injections weekly s.c.) for 7 weeks and 2 injections of vinblastin (0.1 mg/kg BW i.v.) at days 1 and 22.

Six weeks after initiation of α -IFN injections, the patient reported reddening, swelling, induration and itching at insulin injection sites. For further diagnosis he was referred to our department. At this time, he injected 38–48 U/day of regular insulin (depending on blood sugar values) and 40 U/day of basal insulin (1.07–1.21 U insulin/kg BW). Metabolic control was stable (glyc Hb 7.2%, fasting blood glucose levels between 6 and 8 mmol/L, postprandial blood glucose between 5 and 11 mmol/L, no ketonuria).

The treatment with α -IFN was terminated shortly after the onset of this allergic reaction. The signs of early reaction (itching, reddening) then declined.

The patient had no history of allergies and related diseases.

Methods and Investigations

Intracutaneous Insulin Testing

Two units of all usual insulin preparations (Regular, NPH, Lente, Surfen, human, pork, beef; U40) were injected intracutaneously and the skin reaction was followed for 72 h (criteria: reddening, swelling, induration, itching).

Determination of Autoantibodies

Insulin antibodies were determined with an established fluid phase RIA [11]. This assay is also suitable for the detection of insulin autoantibodies in high-risk individuals with predictive value for the development of type 1 diabetes. In parallel an immunoenzymometric assay (SynElisa® Insulin-Antikörper, Elias, Freiburg, Germany) was used. Furthermore, the immunoglobulin classes of the insulin antibodies were determined with different RAST FEIA® (Pharmacia, Sweden): IgE with the CAP system IgE RAST FEIA®, IgG with the IgG RAST FEIA®.

A standard indirect immunofluorescence test was employed on unfixed 4- μ m cryostat sections of monkey tissues (Euroimmun, Lübeck, Germany) for the detection of the following antibodies: antibodies to acinar cells of the exocrine pancreas, antibodies to gastric parietal cells, smooth-muscle antibodies, antibodies to the suprarenal gland and antibodies to skeletal muscles. Rat liver and kidney were used for the determination of antinuclear and antimitochondrial antibodies.

For the determination of islet cell antibodies on human pancreas (blood group 0/d) 1/10 diluted sera (PBS containing 0.14% aprotinin, 2% BSA, 0.1% NaNa, 0.05% Tween 20) were incubated overnight. 1/10 dilutions of sera in PBS were taken to screen for acinar, suprarenal, gastric parietal cell, antimitochondrial, smooth muscle antibodies, and a 1/40 dilution for antinuclear antibodies.

Thyroid peroxidase antibody (anti-TPO) and anti-TSH receptor antibody were determined using commercial RIA test kits (Henning, Berlin, Germany) and glutamate-decarboxylase antibody using an ELISA kit (Elias).

Results

After the intracutaneous injection of insulin, a marked reaction (initial reddening and swelling of 1–2 cm diameter within 1 h, followed by induration of 0.5–1.0 cm diameter and itching up to 72 h) was observed with all tested insulin

preparations, but not with insulin-free injection medium alone. Insulin (auto)antibodies, as defined by a fluid phase RIA, were not detectable at manifestation of diabetes, but were found at high levels during and after cessation of α -IFN treatment. Estimation with the immunoenzymometric assay showed comparable results. Insulin antibodies of both the IgG and IgE subclasses were detectable (table 1). None of the other autoantibodies investigated were found.

Discussion

Besides its other multiple effects, α -IFN can act as an immunostimulating substance. Under treatment with α -IFN, autoimmune reactions, either with or without the development of overt autoimmune diseases, have been observed. Several investigators have detected autoantibodies against: thyroid antigens, nuclear antigens, bile duct epithelia, mitochondrial antigens, red blood cells and smooth muscle cells [1–6]. Thyroid autoimmunity and dysfunction after treatment with α -IFN were first described by Burman et al. [7]. There are large differences between the reports concerning the incidence of different antibodies and the manifestation of autoimmune diseases. The highest incidence figures were observed by Ronnblom [5] in a group of 135 patients with α -IFN-treated carcinoids, where 19% of the patients (25/135) developed an autoimmune disease and 18 of the 25 had thyroid diseases. Mayet et al. [4] and Fentiman et al. [8] also reported a rather high rate of autoimmune phenomena. In contrast, other authors found lower figures of antibody development and even lower incidence rates for overt diseases [9, 10]. It seems that the development of autoantibodies against thyroid tissue and antinuclear antibodies has the highest rate of occurrence after treatment with α -IFN.

The variation in the incidence of autoimmunity found in the different studies may be explained by different underlying diseases and different α -IFN preparations. α -IFN can enhance the immune response by selective inhibition of T suppressor cells [12] as well as by stimulating B cells [13]. Depending on the time sequence of α -IFN administration and sensitization with an antigen, both stimulating and suppressive effects have been observed experimentally [13, 14].

Induction of insulin antibodies and the development of allergic reactions against exogenous insulin were common findings in patients treated with animal insulin, especially when nonpurified preparations were used.

Patients treated exclusively with human insulin (recombinant DNA origin or semisynthetic) can also develop insulin antibodies [15–21]. Compared to treatment with purified porcine insulin, the percentage of patients remaining an-

tibody free after 12 months of treatment with human insulin is significant higher [19]. Despite the development of insulin antibodies in a significant percentage of patients exclusively treated with human insulin, clinically relevant allergic reactions to exogenous human insulin became extremely rare [17, 19, 20, 22, 24, 25]. This was also recently demonstrated for the insulin (Huminsulin, Lilly) used to treat our patient in a cohort of 343 insulin-treated diabetics (Klinischer Bericht zur multizentrischen Anwendungsbeobachtung mit Huminsulin, Lilly Deutschland GmbH) including 31 diabetic patients from our department. Twenty-five of these 31 patients were exclusively treated with human insulin. Only in 2 cases were antibodies found during the follow-up (6 and 12 months) that reacted with human insulin with low binding (0.1 and 0.2%, respectively, bound/total%).

In another study, 72 newly diagnosed type 1 diabetic subjects were followed for at least 12 months. Insulin antibodies were measured with one of the assays used in our case report (SynElisa Insulinantikörper, Elias). The highest antibody level found was 87 U/l. Mean antibody levels after 6 months (9.4±14.8; range: 2–85.4 U/l) and 12 months (11.7±14.6; 2.1–87 U/l) were much lower than in this case report (269.5 U/l) [Krug et al., unpubl. data].

Concerning the IgE insulin antibodies, RAST class 2 is considered to be clearly within the pathological range [22].

High-titer insulin antibodies and insulin allergy are more often observed in patients pretreated with animal insulin and patients in whom therapy was interrupted [20, 23].

Our patient lacks some of the important additional risk factors (genetic background, younger age, interruption of therapy, presence of insulin autoantibodies) [20] for an immune response to insulin. His HLA type is neither associ-

ated with an increased (HLA-DR4) nor a decreased (HLA-DR3) risk of insulin antibody development [26, 21]. Furthermore, insulin therapy was not interrupted since the manifestation of the disease. At clinical onset of diabetes, no insulin (auto)antibodies were detectable.

In our case, insulin was administered before α -IFN. The production of insulin antibodies fits with the hypothesis that α -IFN administration subsequent to sensitization augments the immune response. It is very likely that in our patient the treatment with α -IFN induced (or significantly enhanced) antibody production with subsequent development of an allergy against human insulin [13, 14]. A paraneoplastic effect is rather unlikely, since at the time of diagnosis of the renal carcinoma no insulin antibodies were detectable. The time span between nephrectomy and manifestation of the allergy was more than 6 months. Furthermore, the patient developed his allergy within 6 weeks after institution of the α -IFN treatment.

Autoantibodies against endocrine and other tissues were not detectable, indicating the induction or enhancement of a specific immune response against insulin. We cannot totally exclude a coincidence of α -IFN treatment and the development of an insulin allergy. Unfortunately, no serum sample was available from the time point when α -IFN treatment was started. However, we think that our data are suggestive of a pathogenetic role of α -IFN in the induction of insulin antibodies and allergy in this particular case.

In conclusion, our findings and other observations of α -IFN-induced autoimmune reactions should prompt a very careful use of α -IFN, especially in patients suffering from diseases with autoimmune pathogenesis (such as type 1 diabetes mellitus and autoimmune thyroid diseases) and in

Table 1. Insulinantibodies and different autoantibodies at diagnosis of diabetes mellitus and after α -IFN treatment

Antibody	Method	Normal range	Time course			
			zero ¹	30 weeks ²	36 weeks ³	56 weeks ⁴
I-AB μ U/ml	RIA	<0.56	0.2	26.5	10.3	20.3
I-AB U/ml	SynElisa®	<12	1.3	269.5	227.2	nd
I-AB of IgE sub-class kU/l	RAST-FEIA®	<0.35	<0.35	1.06	0.48	<0.35
RAST class		RAST 0	RAST 0	RAST 2	RAST 1	RAST 0
I-AB of IgG subclass, % binding of an internal standard	RAST-FEIA®	100%	70.2	159	155	116
ICA, JDF-U	IF	0	0	0	0	0
GAD-AB [mGAD-U/ml]	SynElisa®	<1,500	194	422	409	nd

I-AB = Insulin antibody; ICA = islet cell antibody; GAD-AB = glutamic acid decarboxylase antibody; JDF-U = Juvenile Diabetes Foundation-Units.

¹ Diagnosis of diabetes mellitus and renal cell carcinoma.

² 6 weeks after beginning of α -IFN treatment and shortly after development of an insulin allergy.

³ 4 weeks after cessation of α -IFN treatment.

⁴ 24 weeks after cessation of α -IFN treatment.

cases where other potentially immunogenic therapeutic compounds (in this case insulin) are used. The pathogenetic relevance of α -IFN and other cytokines in type I diabetes and a possible acceleration of the disease process should be considered [27–29]. The use of α -IFN in clinical practice should be restricted to the treatment of diseases where evidence of beneficial effects is already established. In the case of α -IFN use in insulin-treated diabetics, regular screening for insulin antibodies and signs of insulin allergy is recommended.

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