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Regression of acanthosis nigricans correlates with disappearance of anti–insulin receptor autoantibodies and achievement of euglycemia in type B insulin resistance syndrome

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Abstract

Autoantibodies directed against specific epitopes in the insulin receptor are rarely the cause of either recurrent hypoglycemia or a severe form of insulin resistance (type B insulin resistance). Type B insulin resistance occurs more commonly in women of African heritage and is frequently associated with a history of other autoimmune diseases. We present the unusual case of a 61-year-old African American woman with a background of autoimmune hypothyroidism and autoimmune hepatitis who developed type 2 diabetes mellitus and marked facial acanthosis nigricans (AN) over a period of weeks. Despite treatment with multiple oral antidiabetic agents, she rapidly developed severe, recalcitrant hyperglycemia and ketoacidosis, requiring hospitalization and intravenous insulin administration for 4 weeks at rates of up to 180 U/h. Immunologic testing revealed a high titer of anti–insulin receptor autoantibodies of both immunoglobulin G and immunoglobulin A classes. After a recurrence of diabetic ketoacidosis despite aggressive management, the patient was treated with a short course of cyclophosphamide; within 10 weeks, she experienced striking improvement of her hyperglycemia as well as marked regression of the AN lesions. Subsequently, the patient also experienced episodes of fasting hypoglycemia, which resolved with a brief course of glucocorticoids. She has since remained euglycemic with no therapy for 5 years. We have documented, for the first time, regression of AN in temporal association with disappearance of circulating anti–insulin receptor autoantibodies and achievement of euglycemia in a patient with type B insulin resistance.

1. Introduction

Type B insulin resistance is an uncommon autoimmune disorder characterized by the production of polyclonal antibodies directed against specific epitopes in the insulin receptor [1]. It typically presents with severe hyperglycemia that is minimally responsive to large doses of insulin but may also cause episodes of hypoglycemia if the responsible immunoglobulins stimulate rather than inhibit the signal-transducing activity of the insulin receptor [2]. Acanthosis nigricans (AN) is a frequent feature of type B insulin resistance, and its extent and severity are often in direct proportion to the degree of insulin resistance [1,2]. We present the unique and instructive case of a 61-year-old woman with type B insulin resistance who required treatment with an immunosuppressive agent to achieve normalization of glycemic control. Remission of her illness was associated with disappearance of both the anti–insulin receptor autoantibodies from her serum and AN from her skin.

2. Case report

A 61-year-old African American woman presented to the emergency center of a community hospital, complaining of blurred vision and polyuria during the previous week. She was found to have modest hyperglycemia, diagnosed with new-onset type 2 diabetes mellitus, given a

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prescription for a sulfonylurea, and sent home. In spite of taking the sulfonylurea, her symptoms worsened progressively, and she subsequently presented to a different hospital 2 days later. She was found to be severely hyperglycemic and was admitted for treatment with intravenous insulin. After 3 weeks, she was discharged from the hospital with a prescription to take isophane insulin suspension 300 U twice daily, insulin lispro 50 U with lunch, pioglitazone 45 mg daily, and metformin 500 mg twice daily. She then presented to the emergency center at Ben Taub General Hospital, Houston, TX, for a second opinion regarding her treatment regimen. We admitted the patient to evaluate her extraordinary insulin requirements.

The patient's medical history was notable for hypertension, primary autoimmune hypothyroidism, and chronic autoimmune hepatitis; the autoimmune hepatitis had been diagnosed by serology and liver biopsy and successfully treated in the past with a course of corticosteroids. Her other medications included levothyroxine, diltiazem, spironolactone, hydrochlorothiazide, ursodiol, and calcium carbonate. Social history was unremarkable and family history unrevealing for any endocrine disorders. Systemic review revealed that the patient had experienced deep darkening and thickening of the skin around both her eyes and the back of her neck over the previous 2 months. Her weight was 80 kg, height 160 cm, and body mass index 31 kg/m^2. Her blood pressure was 109/68 mm Hg, pulse rate 76/min, and temperature 37.2°C. Severe AN was present on the back and sides of the neck, both axillae, and the eyelids and perioribital regions (Fig. 1). The remainder of her physical examination was normal. Laboratory evaluation revealed normal renal and liver functions. The serum concentration of thyrotropin was 1.6 μU/mL (reference range, 0.35-5.5 μU/mL), free thyroxine 1.2 ng/mL (reference range, 0.89-1.76 ng/mL), and hemoglobin A_{1c} 6.3%. Random serum glucose concentration was 149 mg/dL; fasting serum cholesterol level was 134 mg/dL, triglycerides 69 mg/dL, high-density lipoprotein cholesterol 77 mg/dL, and low-density lipoprotein cholesterol 43 mg/dL. A 24-hour urine collection did not show an elevated level of cortisol (36 μg/24 h). The patient was placed on an intravenous infusion of regular insulin, and she achieved blood glucose levels of 120 to 150 mg/dL with an infusion rate of 2 U/h. After 3 days of intravenous therapy, she was successfully transitioned to subcutaneous isophane insulin suspension at a dose of 25 U twice daily and metformin 500 mg twice daily and was discharged from the hospital.

Ten days later, the patient returned complaining of nausea, vomiting, and abdominal pain. Her blood glucose level was 359 mg/dL, serum bicarbonate 15 mEq/L, anion gap 25, and ketones were present in high concentration in her serum and urine (Table 1). She was diagnosed

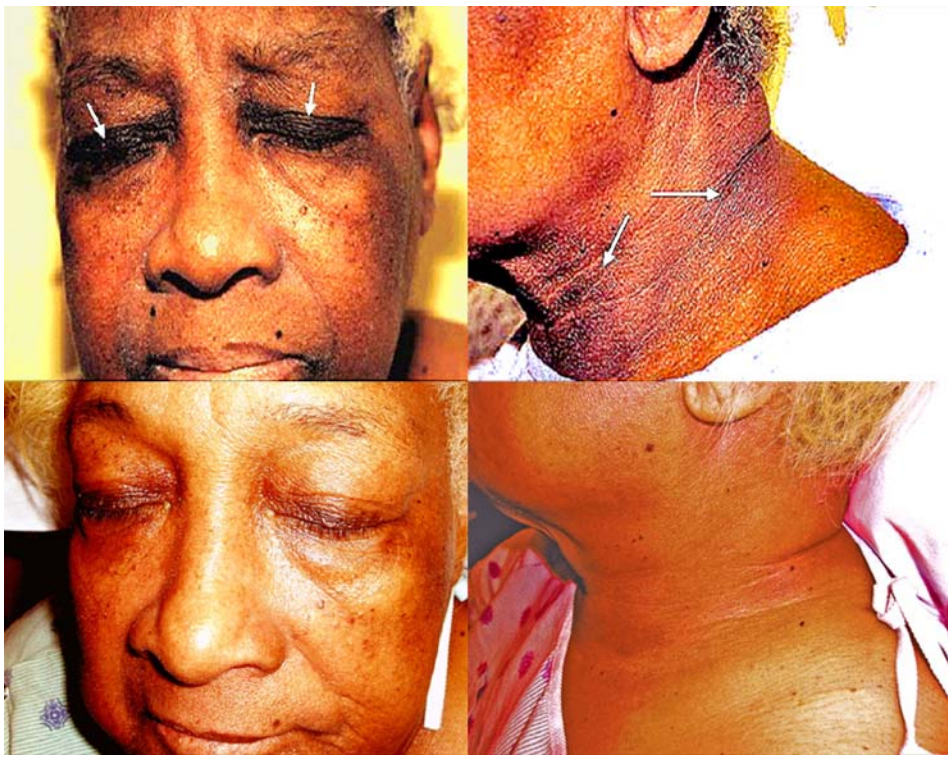

Fig. 1. Top row, Acanthosis nigricans involving the periocular region (unique to type B insulin resistance syndrome) and the neck. The rapid development of AN coincided with the onset of symptoms of hyperglycemia. Bottom row, Regression of AN in temporal association with the decrease in the anti–insulin receptor antibody titer. Insulin resistance and hyperglycemia also improved in concert with the disappearance of antibodies. The regression of acanthosis nigricans is particularly well appreciated in the color version of these images, available online at http://journals.elsevierhealth.com/periodicals/ymeta.

with diabetic ketoacidosis and placed on an intravenous insulin drip. Over the course of the next several days, her insulin requirements escalated rapidly, peaking at a dose of 180 U/h (4320 U/d), to eliminate serum ketones and maintain blood glucose levels in the 200- to 250-mg/dL range. Serum C-peptide level was 34 ng/mL, indicating a severe degree of insulin resistance. The sudden, fulminant onset of diabetes, extreme insulin resistance, and history of autoimmune thyroid and liver disease raised the possibility of anti-insulin or anti–insulin receptor autoantibodies as the cause of the metabolic disorder. Anti-insulin antibodies were absent in the serum (Mayo Medical Laboratories, Rochester, MN); however, anti–insulin receptor antibodies were present in the serum (Dr Phillip Gorden, National Institutes of Health [NIH] laboratories, Bethesda, MD; see Fig. 2B for description). In addition, serum levels of immunoglobulin (Ig) A and IgG were very elevated (1470 mg/dL and 2450 mg/dL, respectively), and positive titers for antinuclear antibodies, anti-thyroidperoxidase antibodies, anti-thyroglobulin antibodies, and rheumatoid factor were documented (Table 1). Metformin was added to her regimen to attenuate insulin resistance. Her hyperglycemia improved, and over the next 4 days, the dose of intravenous insulin was gradually decreased and then discontinued because she was able to maintain blood glucose levels of 100 to 200 mg/dL with no evidence of ketoacidosis. She was discharged from the hospital on a regimen of metformin 850 mg in the morning and 500 mg in the evening.

Table 1
Biochemical and serological evaluation

Laboratory test	Result	Reference range
White cell count	3800/mm^3	4000-11 000
Hemoglobin	10.2 g/dL	12-16
Platelets	380 000/mm^3	140 000-440 000
Sodium	128 mEq/L	135-147
Potassium	4.2 mEq/L	3.5-5.5
Chloride	94 mEq/L	98-108
Bicarbonate	15.6 mEq/L	23-30
SUN	11 mg/dL	8-20
Creatinine	1 mg/dL	0.8-1.5
Glucose	359 mg/dL	70-110
C peptide	34 ng/mL	0-4.0
Albumin	2.9 g/dL	3.5-5.5
Total bilirubin	0.8 mg/dL	0.3-1.0
Serum ketones	Positive	
Urine ketones	Positive	
Antinuclear antibodies	1:80 (nucleolar pattern)	<1:40
Anti-dsDNA	Negative	
Anti-TPO antibodies	Positive	
Antithyroglobulin antibodies	Positive	
Antimitochondrial antibodies	Negative	
Anti–smooth muscle antibodies	Negative	
LKM antibodies	1:40	0-1:39
c-ANCA	Negative	
p-ANCA	Negative	
Sjogren antibodies: SSa	Negative	
Sjogren antibodies: SSb	Negative	
Rheumatoid factor	62 IU/mL	0-20
Erythrocyte sedimentation rate	78 mm/h	0-20
C3	69.5 mg/dL	86-184
CH50	158 U/mL	22-60
IgA	1470 mg/dL	70-307
IgG	2450 mg/dL	613-1295
IgM	132 mg/dL	53-334
Anti-insulin (pork) antibodies	<3%	<3%
Anti-insulin (beef) antibodies	<3%	<3%
Anti-insulin (human) antibodies	<3%	<3%
Insulin receptor antibodies	Positive	

SUN indicates serum urea nitrogen; dsDNA, double-stranded SNA; ANCA, antineutrophil cytoplasmic autoantibody; TPO, thyroid peroxidase; LKM, liver/kidney microsome.

The patient was monitored every 1 to 2 weeks in our diabetes clinic with repeated measurements of blood glucose, fasting C peptide, and metabolic parameters. Gradually, her blood glucose levels rose again, necessitating, at first, increased doses of metformin, then the addition of rosiglitazone, and later, the addition of isophane insulin suspension. Finally, this triple therapy was inadequate, and when the blood glucose levels approached 400 mg/dL (2 months after her last hospitalization), she was readmitted and treated again with intravenous insulin, requiring up to 1440 U/d to maintain blood glucose values in the 250- to 300-mg/dL range. She was then treated with a course of oral cyclophosphamide 150 mg daily for 10 days. Glycemic control improved remarkably after this treatment, and her insulin requirements diminished progressively. She made a full recovery and was finally discharged on a regimen of isophane insulin suspension 60 U in the morning and 25 U at bedtime, insulin lispro with meals, rosiglitazone 8 mg daily, and metformin 850 mg daily.

Over the next 3 months, the patient was able to discontinue insulin treatment with completely normal fasting and postprandial blood glucose levels. Soon thereafter, she began to experience episodes of hypoglycemia at nighttime. She was readmitted to the hospital and documented to have serum glucose values as low as 45 mg/dL in association with symptoms of hypoglycemia. She was treated with a brief course of IV methylprednisolone 120 mg twice daily, and the hypoglycemic episodes resolved completely. Upon discharge, the patient was treated with oral prednisone, which was gradually decreased in dose over a period of 3 weeks and then discontinued.

During careful follow-up in the last 5 years, the patient has had no further recurrences of either hyper- or hypoglycemia (Fig. 2A). She has remained euglycemic on no medications to regulate blood glucose levels, and her most recent hemoglobin A_{1c} values have been 6.1% to 6.4%. During the first few months of this clinical remission, we observed a clear, steady, and significant improvement of her AN lesions (Fig. 1). The resolution of the skin lesions was temporally associated with the disappearance of anti–insulin receptor antibodies on serial serologic testing (Fig. 2B).

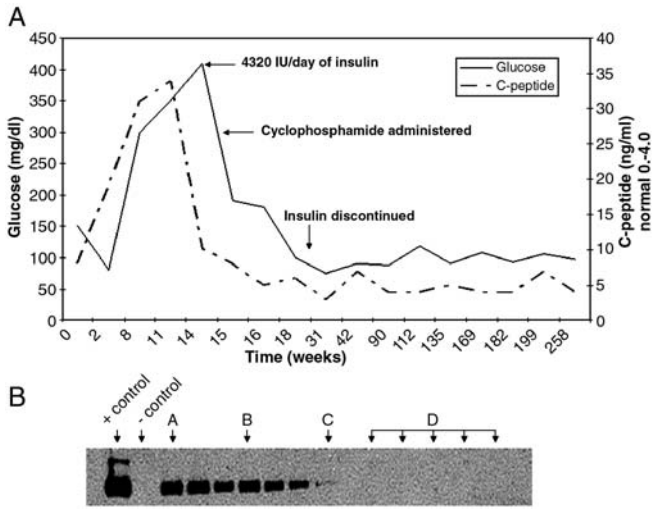

Fig. 2. A, Serum C-peptide and glucose measurements through the course of the patient's illness. Time = 0 denotes initial presentation (x-axis not to scale). B, Serial Western blots demonstrating progressive disappearance of anti–insulin receptor antibodies. (Method: Cos-7 cells were transfected with recombinant human insulin receptors, solubilized for 30 minutes on ice, and insoluble debris was removed by centrifugation at 4°C. One hundred fifty microliters of extract was incubated with 2 μL of the patient's serum overnight at 4°C. The antibody-bound receptors were precipitated with peroxidase-affinity pure F(ab′)2 fragment goat antirabbit IgG-Fc fragment–specific antibody and immunoblotted with anti–insulin receptor β subunit rabbit polyclonal antibody.) A indicates 18 weeks; B, 22 weeks; C, 31 weeks; D, 35-90 weeks from initial presentation.

3. Discussion

In 1961, Field et al [3] described a patient with severe insulin resistance who developed AN in association with greatly increased levels of endogenous insulin. Detailed investigation revealed that the patient's plasma stimulated glucose uptake and glycogen synthesis in isolated rat hemidiaphragm and provoked hypoglycemia in fasted mice; however, the patient's adipose tissue was less sensitive to insulin than similar tissue from healthy or chronic diabetic controls. The investigators speculated that a circulating factor might be the provocative agent but were uncertain as to why both onset and remission of the condition were so abrupt. In 1975, Flier et al [4] investigated binding of [^{125}I]insulin to a variety of normal cell types preincubated with the sera of several patients with insulin resistance and AN. The patients' sera decreased insulin binding by 30%, and this was reversed by the addition of rabbit antiserum to human immunoglobulin, suggesting that the "circulating factor" in this condition might be an antibody that impaired the binding of insulin to its receptor. In addition, the absence of anti-insulin antibodies suggested that the cause of the disorder was an immunoglobulin directed specifically against the insulin receptor. The authors later termed the syndrome *type B insulin resistance*, to distinguish it from the clinically similar type A syndrome, in which insulin resistance results from a primary structural defect in the insulin receptor due to a genetic mutation [5]. Later, immunoprecipitation experiments by Flier et al [6] demonstrated that the antibodies were predominantly of the IgG class, with a smaller subfraction of IgM forms. Reaction to antisera against both κ and λ light chains indicated that the antibodies were polyclonal. Further exploration of the heterogeneity of the immunoglobulins confirmed their variable capacity to either block or activate the insulin receptor [7]. Although it is clear that the target epitope is a constituent of the insulin receptor heterodimer protein, the antibodies likely react to multiple different antigenic sites on the receptor complex [7]. Zhang and Roth [8] have described a region containing residues 450 to 601 of the α subunit that may be a major recognition site for anti–insulin receptor antibodies. This region corresponds to an extracellular region of the insulin receptor α subunit that is just adjacent to the cell membrane.

Type B insulin resistance is a rare disorder, and most reports in the literature are limited to single case descriptions or small case series. One of us (EO) has recently reported the common features and natural history of the condition in a series of 24 patients followed at the NIH for the past 28 years [1]. It most often occurs in the third to fifth decades of life and is more common in women (83%) and in persons of African heritage (88%). There is usually a history of autoimmune disease, particularly systemic lupus erythematosus, and this precedes the onset of metabolic derangement in 95% of cases. Patients may present with hyperglycemia (80%) or hypoglycemia (20%), and up to 14% of those with initial hyperglycemia develop symptomatic hypoglycemia at a later time. The degree of hyperglycemia varies from moderate to severe, but its appearance is invariably sudden and associated with preceding weight loss. Circulating levels of endogenous insulin are high (>200 μU/mL), and up to 53% of female patients may have evidence of elevated testosterone associated with heterogeneous cystic enlargement of the ovaries. The average daily dose of exogenous insulin in the NIH series was 5100 U [1],

but doses in excess of 177 000 IU/d have been described in prior reports [9].

Acanthosis nigricans was first described in 1890 [10], and there have since been various attempts at classification, although the most convenient is a simple division into 2 categories based upon malignant or benign etiology [11]. Acanthosis nigricans is associated with a variety of endocrine disorders [11] and occurs in up to 88% of patients with type B insulin resistance [1]. It is a disorder of the skin characterized by symmetrical, poorly marginated plaques with increased skin markings and a light brown to black velvety appearance [12]. Acanthosis nigricans typically occurs in the nape of the neck, axillae, groin, antecubital regions, popliteal fossae, and mucocutaneous surfaces of the lips and vulva [12]. In patients with type B insulin resistance, there is a unique periocular distribution that is not seen in other more gradually progressive forms of insulin resistance [1]. The common histologic appearance in all cases of AN is epidermal papillomatosis and hyperkeratosis, with occasional melanotic hyperpigmentation in the stratum corneum [12]. These changes may occur in response to activation of 1 of 3 different sets of cellular receptors: epidermal growth factor receptor, fibroblast growth factor receptor, and insulinlike growth factor 1 receptor (IGFR) [13]. Each set of receptors is a member of the tyrosine kinase receptor superfamily and has been demonstrated to have mitogenic and antiapoptotic effects on keratinocytes, which may explain why distinct etiologies, such as malignancy and insulin resistance, can produce a similar phenotype [14]. Insulinlike growth factor 1 receptor is expressed on the surface of human keratinocytes and fibroblasts [15]. Insulin has been demonstrated to cross the dermal-epidermal junction to reach keratinocytes [16], and whereas at low concentrations, it binds preferentially to its own receptor, in higher concentrations (as in severe insulin resistance), insulin can significantly bind to and activate IGFR [17]. Binding of insulin to IGFR promotes proliferation of fibroblasts and keratinocytes, leading to AN [12,17].

Another peculiarity of the development of AN in type B insulin resistance is its abrupt onset corresponding to the occurrence of symptomatic hyperglycemia. A relationship between AN and the clinical course of insulin resistance in the type B syndrome has been observed since the original report by Field et al [3] in 1961. However, to our knowledge, the documented disappearance of circulating anti–insulin receptor autoantibodies in temporal association with the resolution of AN lesions and full remission of the condition has not been reported previously. The phenomenon we have observed goes further to fulfill Koch postulates with regard to an etiologic role for anti–insulin receptor autoantibodies in the pathogenesis of AN.

Metformin and thiazolidinediones have been used to improve insulin sensitivity in patients with type B insulin resistance, but the results have been mixed [1,18]. Immunomodulating agents have been tried to inhibit production of the autoantibodies, and some of these treatments have been associated with reduction in antibody titers and restitution of glucose homeostasis [19-21]. In the NIH series [1], results from long-term follow-up were available on 18 of the 24 patients: 6 of these 18 patients (33%) experienced spontaneous reduction of the antibodies over a period of 11 to 48 months and achieved euglycemia; the remaining 12 patients were treated with high doses of corticosteroids, cyclophosphamide, cyclosporine A, azathioprine, or plasmapharesis. Half of those treated with immunosuppresants became euglycemic within 6 weeks, whereas the remainder continued to have hyperglycemia. In patients who initially presented with or later developed hypoglycemia, high doses of corticosteroids were effective in the acute phase, improving blood glucose levels in many patients within 24 hours. However, there is very limited information on the long-term benefits of corticosteroid therapy for hypoglycemia in patients with anti–insulin receptor autoantibodies.

4. Conclusion

On the basis of her age, ethnicity, sex, history of autoimmune disease, periocular AN, and abrupt onset of intractable hyperglycemia in association with a high serum titer of autoantibodies to the insulin receptor, our patient fits the archetypal model of type B insulin resistance. Her case contributes to the small body of literature on the potential for patients who develop anti–insulin receptor autoantibodies to present at different times with both hyper- and hypoglycemia. The clinical course and serial fasting serum C-peptide levels clearly document the changing pattern of insulin sensitivity (and corresponding hyper- or hypoglycemia) caused by alternating stimulatory and inhibitory antibody activity upon the insulin receptor. The patient had abrupt onset of AN due to the development of this acquired form of severe insulin resistance. Hyperinsulinemia, a hallmark of insulin resistance, is believed to activate mitogenic and antiapoptotic pathways through epidermal cell receptors such as insulin-like growth factor 1, resulting in proliferation of keratinocytes and development of AN. Detailed, serial measurements over a period of 6 years permitted us to correlate the metabolic abnormalities, serum autoantibody titers, and presence of AN during different phases of her illness. Remarkably, clinical remission after treatment with cyclophosphamide was associated temporally with disappearance of antibody from the serum and concomitant, significant improvement in the skin lesions of AN. We believe that this report is the first to document a clear relationship between disappearance of the antibodies and regression of AN, thus confirming that the development of AN is mechanistically linked to insulin resistance. We propose that improvement in AN may serve as an effective surrogate marker of declining anti–insulin receptor antibody levels and improving insulin sensitivity in patients with type B insulin resistance.

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