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CASE REPORT

Protamine-containing insulin allergy and renal dysfunction in a patient with type 2 diabetes

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ABSTRACT

An 87-year-old woman with type 2 diabetes noticed a red itchy rash at the insulin injection sites 3 weeks after initiation of premixed insulin therapy. Laboratory data at that time showed marked eosinophilia and progression of renal dysfunction. Insulin treatment was discontinued, and antidiabetic oral drugs were used, as well as intravenous injection of dexamethasone. Her skin lesions disappeared, and both eosinophilia and renal dysfunction gradually improved. The results of skin prick tests and measurement of specific immunoglobulin E antibodies suggested that the insulin allergy was caused by protamine. Although cases of insulin allergy associated with renal dysfunction are rare, we must be aware, especially for elderly patients with poor renal function in the first application of insulin.

INTRODUCTION

Although the widespread use of recombinant human insulin and human insulin analog in patients with diabetes has greatly reduced the incidence of insulin allergy[1–3], cases with insulin allergy continue to occasionally present in the clinic. Insulin allergies are varied and can be local or systemic, as well as immediate or delayed[1,4]. Reports of insulin allergy associated with renal dysfunction are extremely rare. We report herein the case of a patient with type 2 diabetes who showed skin rash, marked eosinophilia and progression of renal dysfunction after insulin therapy.

CASE REPORT

An 87-year-old woman had been suffering from type 2 diabetes since 1992. She was intermittently treated with oral hypoglycemic agents and had not been monitoring her blood glucose. The treatment with insulin aspart 30 (Novo Nordisk, Bagsvaerd, Denmark) started when she was admitted to the Neurology Department at Nanjing Medical University affiliated Wuxi People's Hospital, Jiangsu Wuxi, China, because of cerebral infarction. Three weeks later, she noticed a red itchy rash occurring several hours after insulin injection at the injection sites, but neither treatment for the skin lesions nor insulin cessation was practiced. Two months later, for management of her condition, she was admitted to the Endocrinology Department. She had a 50-year history of hypertension leading to renal complication (urinalysis white blood cells [WBC] 0/μL, red blood cells 3.2/μL, protein (+); serum urea 12.7 mmol/L; serum creatinine 203.3 μmol/L before insulin injection). She had been taking amlodipine, pravastatin and aspirin. There was no history of drug-induced or alimentary allergy.

At the time of admission, the patient had an intradermal induration ranging from 1 cm to 3 cm in diameter at the insulin injection sites. She had no diabetic retinopathy and neuropathy. Her laboratory data showed: peripheral blood WBC 8,900/mm^3, eosinophils 9.0%; fasting blood glucose 132.5 mg/dL; glycated hemoglobin 10.9% (96 mmol/mol); urinalysis WBC 283.2/μL, red blood cells 25.9/μL, protein (+), glucose (–), ketone (–); negative urine culture; 24 h urine protein 0.36 g; serum urea 14.8 mmol/L; serum creatinine 250.5 μmol/L.

After admission, blood sugar was controlled by subcutaneous injection of insulin aspart 30. On day 3, insulin aspart 30 was replaced by human insulin 30R (Novo Nordisk, Bagsvaerd, Denmark) because of the continuous emergence of a new rash at the insulin injection site. Then, the rash began to subside with oral ketotifen and topical corticosteroid ointment. However, biochemistry suggested a gradual deterioration of renal function. On day 9, there erupted similar skin lesions at the insulin injection sites, and laboratory data at that time showed progression of renal function (serum urea, 25.0 mmol/L; serum creatinine, 362.5 μmol/L) and marked eosinophilia (WBC 10,600/mm^3, eosinophils 15.4%), so human insulin 30R was discontinued, and repaglinide (6 mg/day) treatment were

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initiated, as well as intravenous injection of dexamethasone (5 mg/day). On day 11, skin lesions began to disappear, and eosinophils decreased to 0.10%, but renal function (serum urea, 29.5 mmol/L; serum creatinine, 379.9 μmol/L) did not improve. To restore normal eosinophils, dxamethasone was reduced to 2.5 mg/day. Glutathione was applied intravenously to protect renal function. On day 13, the skin lesions disappeared completely, the eosinophils were maintained in the normal range and serum creatinine began to decline, so dexamethasone was stopped. On day 23, renal function (serum urea 14.4 mmol/L; serum creatinine 238.9 μmol/L) returned to a similar level to that before insulin therapy (Table 1). During hospitalization, immunological tests showed that antinuclear antibody, anti-extractable nuclear antigen antibody spectrum, anti-proteinase 3 antibody, anti-myeloperoxidase antibody and anti-glomerular base membrane antibody were negative, and immunoglobulin (Ig; IgA, IgM, IgG), complement (C3, C4), C-reactive protein and rheumatoid factor were within the normal range. Serum total IgE (68 U/L) was normal. IgE specific for human insulin was <0.35 UA/mL. With the patient's consent, skin prick tests were carried out after her renal function recovered. The results showed that protamine caused a skin reaction, whereas short-acting human insulin (insulin R) or insulin analog (aspart) did not.

Two months later, the patient consulted our hospital as an outpatient. Laboratory data showed: peripheral blood WBC 7,900/mm^3, eosinophils 1.0%; urinalysis WBC 17.1/μL, red blood cells 4.3/μL, protein (–), glucose (–), ketone (–); serum urea 6.6 mmol/L; serum creatinine 235.3 μmol/L; fasting blood glucose 128.7 mg/dL; glycated hemoglobin 10.1% (87 mmol/mol); and serum C-peptide 7.71 ng/mL (fasting), 9.25 ng/mL (2-h postprandial). According to the result of serum C-peptide, the patient's endogenous insulin secretion was preserved with insulin resistance, and repaglinide was continued to control the blood sugar.

Recently, we acquired information that the patient had passed away, and before her death she was treated with a short-acting insulin without insulin allergy for half a year, which was provided by her family.

DISCUSSION

Because of that patient's clinical features (rash, urine WBC, eosinophilia, deterioration of renal function) acute interstitial nephritis (AIN) was suspected[5]. After withdrawal of insulin and corticosteroid therapy, her renal function returned to basal. Therefore, we concluded that renal dysfunction was induced by her insulin allergy. There is no relevant literature description, except a similar case reported by Naqai *et al.*[6] in 2001. Common characteristics of two cases were elderly patients, pre-existing kidney disease, parallel changes of renal dysfunction progression with eosinophilia and the key treatment of stopping insulin. We speculate that eosinophilia can be the signal of kidney damage induced by insulin allergy, and that old age and pre-existing kidney disease seem to be predisposing factors for this condition[7].

In their case, Naqai *et al.*[6] confirmed the type of insulin allergy as immediate-type IgE-mediated reactions by skin prick test and increased insulin-specific IgE antibody. In the present case, because of patient's insulin-specific IgE and the skin prick test results, we speculated that protamine was the cause of her insulin allergy. This was further confirmed by the recent information that she was treated with a short-acting insulin without insulin allergy for half a year. Renal pathology showed that cell-mediated immune mechanisms seemed to be more important than humorally-mediated mechanisms in the pathogenesis of AIN[5]. However, renal biopsy was not made in the present case, because of the patient's refusal. Because of a delayed onset after insulin injection and induration at the injection site, we tend to consider the type of insulin allergy in our case as delayed type hypersensitivity reactions[8].

Table 1 | Laboratory data after admission of the patient

Day after admission	Blood routine test		Renal function	
	Leukocyte ($\times 10^9$/L)	Eosinophil (%)	Serum urea (mmol/L)	Serum creatinine (μmol/L)
Reference normal values	4–10	0.5–5	1.9–7.2	50–120
1	8.90	9.00	14.80	250.50
3	–	–	13.80	255.80
5	–	–	17.50	290.00
8	–	–	22.30	338.20
9	10.60	15.40	25.00	362.50
11	10.20	0.10	29.50	379.90
13	11.40	0.30	32.20	349.00
16	15.50	3.10	29.90	292.00
18	12.60	3.00	21.10	272.20
23	9.40	4.70	14.40	238.90

DISCLOSURE

The authors declare no conflict of interest.

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