

Immediate-Type Allergy against Human Insulin Associated with Marked Eosinophilia in Type 2 Diabetic Patient

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Abstract. We describe a type 2 diabetic patient who showed immediate-type allergy against human insulin associated with marked eosinophilia at initial insulin therapy. Three months after initiation of insulin therapy, he noticed itchy skin wheals at the site of the insulin injection. Laboratory data at that time showed marked eosinophilia (2512/mm³) and progression of renal dysfunction. Skin test with semisynthetic human insulin and protamine sulfate resulted in local immediate skin reactions such as itchy erythema and wheals. Histopathology of the biopsy specimen from skin showed perivascular infiltration of lymphocytes and numerous eosinophils in the dermis and subcutaneous fat. Although the titer of total IgE antibody was within normal range, that of insulin-specific IgE antibody was high. Insulin administration was discontinued to preserve his insulin secretion, and stable control of his hyperglycemia was obtained by initiating nateglinide treatment (360 mg/day). His itchy skin lesions disappeared within two weeks after cessation of the insulin therapy and both eosinophilia and renal dysfunction gradually improved. Although the widespread use of human insulin in diabetic patients has greatly reduced the incidence of insulin allergy, the possibility of human insulin allergy should be kept in mind when initiating such therapy.

Key words: Insulin allergy, Human insulin, Eosinophilia, Type 2 diabetes mellitus, Renal dysfunction
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THE widespread use of human insulin in diabetic patients has greatly reduced the incidence of insulin allergy, especially at the initial insulin therapy [1]. There are only a few reports in the English literature on diabetic patients with immediate-type allergies against human insulin [2–6]. To our knowledge, there are no reports of immediate-type allergy against human insulin with marked eosinophilia. We report here a very rare case of type 2 diabetes mellitus with an immediate-type allergy against semisynthetic human insulin associated with marked eosinophilia at the initial insulin therapy.

Case Report

An 81-year-old male patient was admitted to our hospital in June 2000 because of poor glycemic control and progression of renal dysfunction. He had been initially diagnosed with diabetes mellitus in 1969. Although he had been treated with a sulphonylurea agent since 1984, he had never been previously treated with insulin. In 1971 he started taking anti-hypertensive agents to control his hypertension. He underwent a bypass operation for stenosis of the right femoral artery in January 1999 and was diagnosed as having angina pectoris in January 2000. He never exhibited any anaphylactic reactions or immediate skin reaction such as urticaria. Despite of submaximal dose of gliclazide (120 mg/day) initiated from January 1999, his glycemic control deteriorated (plasma glucose level, 400 mg/dl; HbA1c, 8.1% in June 2000) and his renal dysfunction progressed for three months (serum creatinine level rose

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from 2.0 to 2.7 mg/dl).

On admission in June 2000, his blood pressure was 138/80 mmHg and his pulse 78 beats/min. His body mass index was 22.0 kg/m² (height 155 cm and weight 52.8 kg). He showed no facial or pretibial edema. His diabetes was complicated with background retinopathy, mild neuropathy, and advanced nephropathy (chronic renal failure state). Laboratory data revealed a white blood cell count of 8,800/mm³, with 7.3% eosinophils. Serum creatinine was 2.7 and serum urea nitrogen was 52 mg/dl. In spite of his advanced age, he started semisynthetic human insulin therapy, i.e., Penfill R (Novo Nordisk, Denmark) before each meal and Penfill N (Novo Nordisk) at bedtime, because of poor glycemic control and advanced renal dysfunction. Shortly after initiation of insulin treatment, his glycemic control showed a marked improvement (Fig. 1).

However, three months later, he noticed itchy skin wheals at the insulin injection sites without generalized allergic reactions. When he visited the hospital for examination at this time his blood pressure was 143/75 mmHg and his pulse was 83 beats/min. His weight was 54.3 kg. He showed no facial edema, pretibial edema, or lymphadenopathy. Laboratory data on September 22, 2000 showed marked eosinophilia (2512/mm³) and elevated serum creatinine (4.2 mg/dl) (Fig. 1). Therefore, he was readmitted to our hospital. Laboratory data on admission revealed normal adrenocortical function (plasma ACTH, 31 pg/ml; plasma cortisol, 9.4 µg/dl in the morning). No eggs from parasites were detected in his stool. Bone marrow showed no hematological disorders. His urinary excretion of C-peptide was 118.4 µg/day. There were various-sized insulin lipodystrophic lesions and itchy skin wheals at the insulin

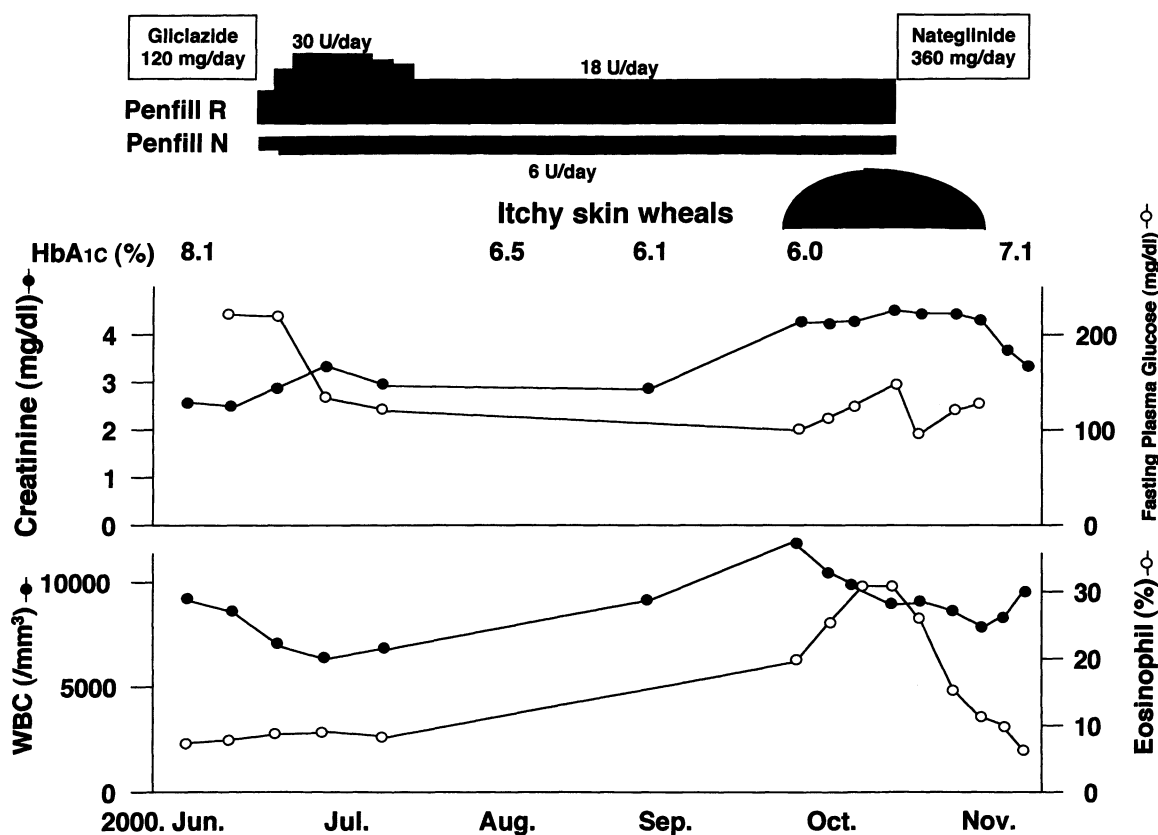


Fig. 1. Clinical course of type 2 diabetic patient with an immediate-type insulin allergy against human insulin associated with marked eosinophilia. Three months after initiation of insulin therapy, itchy skin wheals appeared at the site of the insulin injection. Laboratory data at that time showed marked eosinophilia and progression of renal dysfunction. The itchy skin lesions disappeared within two weeks after cessation of insulin therapy, and both eosinophilia and renal dysfunction gradually improved.

injection sites on his abdomen. Taking into account his clinical course, we suspected an immediate-type allergy against insulin. To evaluate insulin allergy, intradermal skin tests were performed with Penfill R, Penfill N, protamine sulfate, and 0.9% NaCl. Skin test with semisynthetic human insulin and protamine sulfate resulted in local immediate skin reactions such as itchy erythema and wheals. Next, we took a skin biopsy from one of the fresh itchy wheals. Histopathology of the biopsy specimen showed perivascular infiltration in the dermis and subcutaneous fat. Infiltration consisted of lymphocytes and numerous eosinophils (Fig. 2). Although the titer of total IgE antibody was within normal range (IgE: 90 IU/ml), that of insulin-specific IgE antibody (measured by Pharmacia CAP system) was high (6.75 UA/ml; normal range, <0.34 UA/ml). To our regret, the

assessment of anti-insulin total IgG and IgG subclasses was not performed. ^{125}I -insulin-binding rate was 68.8% (normal range: 0–15%). However, the lymphocyte stimulation tests by Penfill R and Penfill N were both negative. Since his insulin secretion was preserved, insulin administration (a total of 24 U/day) was discontinued and nateglinide (360 mg/day) was administered in its place to control his hyperglycemia. His itchy skin lesions disappeared within two weeks from cessation of the insulin therapy and his eosinophilia gradually improved. Glycemic control was stably maintained by nateglinide alone without adverse effects. Interestingly, his renal dysfunction ameliorated after cessation of insulin therapy (serum creatinine, 3.3 mg/dl on November 16, 2000) (Fig. 1).

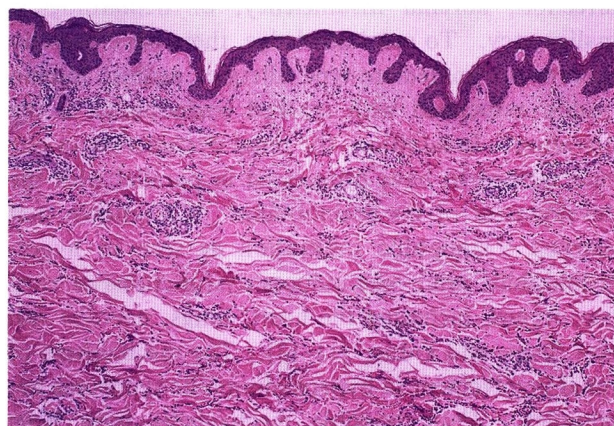
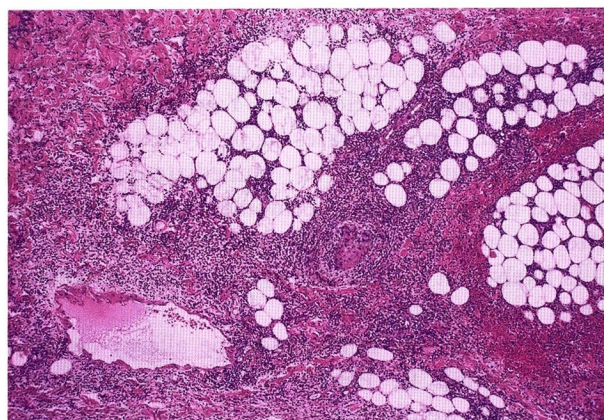
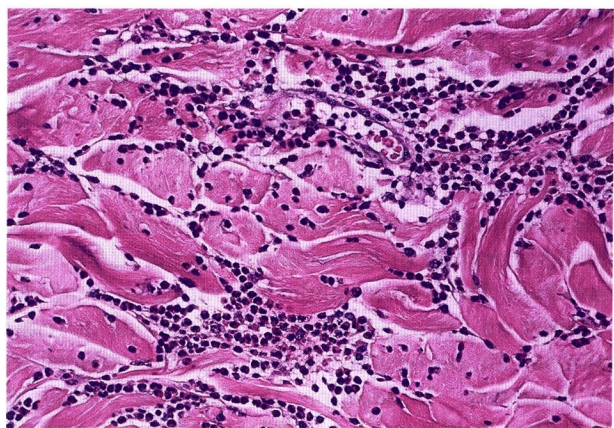
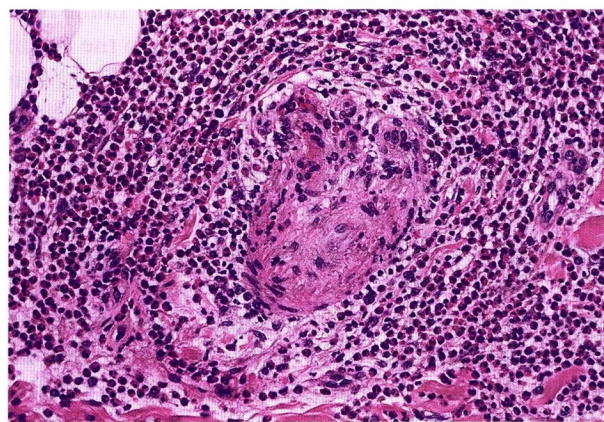
**a****c****b****d**

Fig. 2. Histopathology of the biopsy specimen from one of the fresh itchy wheals (hematoxylin and eosin). Lymphocytes and numerous eosinophils infiltrated the dermis (a, $\times 40$; b, $\times 200$) and subcutaneous fat (c, $\times 40$; d, $\times 200$).

Discussion

Before the advent of human insulin, insulin allergy against bovine and porcine insulin was a common finding manifested by 5–10% of diabetic patients at the initial phase of therapy [7]. However, the widespread use of human insulin in diabetic patients has greatly reduced the incidence of insulin allergy, especially at the initial insulin therapy [1]. Thus, only a few case reports on immediate-type allergies against human insulin have been published in the literature [2–6].

Allergy to insulin may be manifested as a discrete local dermal reaction or as a generalized reaction with concurrent local skin reactions. Our case showed insulin lipodystrophy and itchy skin lesions only, with no urticaria or anaphylactic reactions. Thus, the insulin allergy of our case may have been a local dermal allergy. Most cases of insulin allergy occur two weeks after initiation of insulin therapy [2–4]. Our case noticed itchy skin wheals at the insulin injection sites three months after initiation of insulin therapy. However, Yamagishi *et al.* and Nagai *et al.* reported cases of newly diagnosed diabetes associated with an immediate-type allergy against human insulin two months and four months after the initial insulin treatment, respectively [5, 6]. It is likely that insulin allergy will occur at different times in different patients.

In our case, the immediate-type allergy occurred against Penfill R, Penfill N, and protamine sulfate. Since we did not use an insulin allergy skin-testing kit containing different insulins, we could not clearly identify the causal substance for immediate-type allergy among the various additives in the insulin preparations (protamine sulfate, zinc suspension, NPH suspension and preservative agents such as paraben, cresol, and phenol). However, local skin allergic reaction to Penfill R not containing protamine sulfate and the fact that insulin specific IgE antibody was positive highly indicated the presence of a specific allergy to human insulin in this patient. The amino acid sequence of semisynthetic human insulin is identical to that of endogenous native insulin, and the immediate-type allergic reaction against this insulin may have been due to a tertiary structural change during the unphysiologic subcutaneous administration [5]. The immediate-type allergy appears to be the result of a predisposition

toward Th2-type responses, which result in the formation of large quantities of allergen-specific IgE [8, 9]. Unfortunately, we could not measure the secretion of cytokines such as IL-4, IL-5, and TNF- γ , from his lymphocytes in vitro. In addition, recent studies suggest that insulin allergy is under genetic control. For example, the immune response to insulin is associated strongly with HLA-DR4 but weakly HLA-DR2 and DR3 [1, 10]. To our regret, HLA phenotyping of our case was not investigated, so it remains unclear whether he is genetically predisposed to his allergy.

The most interesting finding in our case was the association with marked eosinophilia. For two reasons, we concluded that his eosinophilia must have been induced by his insulin allergy. Firstly, his eosinophilia improved after the cessation of insulin therapy, and secondly, he had no other disorders that could have induced eosinophilia, such as parasitic infection, adrenal insufficiency, or hematological malignancy. To our knowledge, there have been no reports on immediate-type allergies against human insulin associated with marked eosinophilia in the literature. In addition, the renal dysfunction in our case seemed to have progressed in parallel with the development of his eosinophilia. It is known that marked eosinophilic infiltration as seen in hyper-eosinophilic syndrome induces dysfunctions of various organs, including the heart, lungs, nervous system, liver, and kidney [11–13]. The mechanisms of renal involvement in hypereosinophilic syndrome are complex. Four possible mechanisms have been identified: 1) deleterious effects of eosinophil granules, 2) microemboli from the heart in patients presenting fibroplastic endocarditis or eosinophilic myocarditis, 3) immuno-allergic process leading to deposition of immune complexes in glomeruli, and 4) release of cytokines and other mediators such as leukotriens [13]. Considering that his renal function was ameliorated after cessation of insulin therapy, the deterioration of his renal dysfunction is likely to have been due to eosinophilic infiltration into kidney.

Based on urinary excretion of C-peptide at readmission, his endogenous insulin secretion seemed to be preserved. In addition, the fact that a total of 24 U/day insulin were needed for glycemic control suggested the presence of insulin resistance. Since we did not measure his urinary excretion of C-peptide before initiation of insulin therapy, it is unclear when

insulin resistance was developed. However, we could not deny the possibility that insulin resistance in our case might be due to an anti-insulin antibody. In fact, there are three case reports that insulin allergy and resistance developed in patients whose initial form of insulin therapy was human insulin [2, 11, 14].

Most patients with local dermal reactions will improve within 30–60 days if they continue to use the insulin causing the allergy [15]. However, if reactions continue for more than 14 days, the following strategies should be considered: 1) desensitization with human insulin [16], 2) co-administration with glucocorticoid plus antihistamines [14], 3) continuous subcutaneous insulin infusion [6, 17], and 4) administration of human insulin analogue in place of human insulin [18, 19]. Since our case was advanced in age and we could not use insulin analogue at that time, it was difficult to implement these strategies.

Because his endogenous insulin secretion was preserved, we decided to use nateglinide, a fast-acting short-duration insulinotropic agent with a short half-life that we thought might improve safety and efficacy in treatment of an aged case of type 2 diabetes mellitus with chronic renal failure. Surprisingly, our case achieved satisfactory glycemic control by nateglinide without prolonged hypoglycemia. However, we still have no precise explanation as to why nateglinide exhibited a hypoglycemic action comparable to that of a moderate dosage of insulin in our case.

In summary, we reported here a very rare case of type 2 diabetes mellitus with immediate-type allergy against human insulin associated with marked eosinophilia. The possibility of human insulin allergy should be kept in mind when initiating human insulin therapy.

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