

Case Report

Development of insulin allergy after bone marrow transplantation

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Abstract

Background Insulin allergy is a not uncommon condition even though human insulin and insulin analogues are widely used. However, the development of insulin allergy after bone marrow transplantation has not been reported.

Case report A 44-year-old Japanese woman had aplastic anaemia and secondary haemochromatosis. She was diagnosed with having diabetes at age 32 years and had been treated with human insulin. At age 34 years, bone marrow transplantation was performed. One year later, a rash and urticaria appeared immediately after insulin injections. Intracutaneous tests were positive for both human insulins and analogues, whereas the test for protamine was negative. Furthermore, an IgE-radioallergosorbent test against insulin was positive. Thus, we diagnosed the patient with having an IgE-mediated type I allergy against insulin. Insulin therapy with insulin aspart, which showed the least skin reaction, was continued and the insulin allergy disappeared in 7 years.

Conclusions This is the first description of insulin allergy after bone marrow transplantation. Our case underscores the effects of bone marrow cells on IgE-mediated type I allergy for insulin.

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Introduction

Insulin allergy is a not uncommon condition even though human insulin and insulin analogues are widely used [1–3]. Allergy to recombinant human insulin or insulin analogues has been described [4–6]. Insulin allergy exhibits a wide range of clinical features, from local injection reactions to severe generalized anaphylaxis. When local injection reaction appears immediately after the injection of insulin, IgE-mediated type I allergy is suspected and an intracutaneous test using insulin preparations and the measurement of specific IgE antibodies against insulin are helpful for the diagnosis of insulin allergy [7]. Insulin allergy has been reported in various conditions; however, we present, to our knowledge, the first case of insulin allergy after bone marrow transplantation.

Case report

The patient was a 44-year-old Japanese woman who had aplastic anaemia from age 16 years and secondary haemochromatosis attributable to frequent transfusion. She was

diagnosed with having diabetes, classified as ‘other specific type’ as a result of haemochromatosis at age 32 years, and had been treated with human insulin (humulin R and N; Eli Lilly Japan, Kobe, Japan). At that time she did not exhibit any indications of insulin allergy. At age 34 years, an allograft bone marrow transplantation between non-relatives was performed. The unrelated donor, matched for human leukocyte antigen (HLA), was healthy and did not have diabetes or allergy. The conditioning regimen consisted of 150 mg/m² of fludarabine, 70 mg/m² of melphalan and 30 mg/m² of anti-thymocyte globulin. The patient received total body irradiation of 4 Gy. For graft-versus-host disease (GVHD) prophylaxis, cyclosporine A and methotrexate were administered. Acute graft-versus-host disease occurred at day 18 after bone marrow transplantation and the patient was treated with 50 mg/day of prednisolone, which was tapered to 5 mg/day as a maintenance dose. Thirty units of human insulin were injected daily and skin rashes were not observed at injection sites.

One year later, a rash and urticaria appeared immediately after insulin injections. After we suspected insulin allergy and changed humulin R to insulin lispro, skin reactions ameliorated, but had not disappeared altogether. At the discontinuation of corticosteroid therapy at age 39 years, anaphylaxis occurred: hypotension, and skin rash and urticaria not only at

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the injection site but also throughout the patient's body. Detailed examinations of insulin allergy were performed. Intracutaneous tests were positive for both human insulin (humulin R and N) and analogues (insulin aspart, insulin lispro and glargine), whereas the test for protamine was negative. The patient did not have eosinophilia. Her IgE concentration was normal (56.5 IU/ml, normal range < 173 IU/ml), but the IgE-radioallergosorbent test against insulin was positive (12.0 UA/ml, normal range < 0.34 UA/ml; capsulated hydrophilic carrier polymer class was 3). Thus, we diagnosed her with having IgE-mediated type I allergy against insulin. Anti-glutamic acid decarboxylase antibody was negative. As insulin aspart caused the least skin reaction, insulin therapy with insulin aspart four times per day was continued. The patient exhibited erythema in her face and body and a diagnosis of chronic graft-versus-host disease was established by a skin biopsy. Prednisolone (20 mg/day) was then administered and tapered to a maintenance dose of 5 mg/day. Total daily insulin aspart dose was modified between 19 and 42 U, depending on the dosage of prednisolone and physical activity. IgE-radioallergosorbent test levels had gradually declined to normal range. Skin reactions finally disappeared in 7 years.

Discussion

Our case is the first description of insulin allergy after bone marrow transplantation. In the majority of cases, insulin allergy has an immediate hypersensitivity reaction, i.e. type I. The binding of IgE to insulin results in the formation and release of inflammatory mediators from mast cells, leading to erythema, itching and urticaria [1–3]. This may occur as a biphasic reaction, with immediate itching and burning at the injection site, followed by a sustained induration and generalized reaction 4–8 h later. Type III immune complex-mediated reactions [8] or type IV hypersensitivity [9] may occur as insulin allergy. Laboratory findings suggest that our patient had IgE-mediated type I insulin allergy.

In our patient, the development of insulin allergy was associated with bone marrow transplantation. The onset of insulin allergy in most cases is within the first 6 months of insulin treatment [1,2,7]; however, the patient had not exhibited insulin allergy over a 2-year period of insulin treatment before bone marrow transplantation. It was 1 year after bone marrow transplantation that she developed insulin allergy. One possibility is that the donor might have insulin allergy and insulin-specific IgE hypersensitivity was transferred by bone marrow transplantation. Allergen-specific IgE hypersensitivity is shown to be transferred by bone marrow transplantation [10,11]: Tabbara *et al.* reported the acquisition of vernal and atopic keratoconjunctivitis after bone marrow transplantation [12]. However, this was not the case, because the donor had neither diabetes nor allergy. The donor did not have insulin allergy at the time of bone marrow transplantation, indicating that hypersensitivity to insulin was not passively transferred from the donor to the patient. Another possibility is that the patient

newly acquired insulin allergy after bone marrow transplantation, irrespective of the donor. Allergy can develop after bone marrow transplantation not only from an atopic donor, but also from a non-atopic donor [13]. Presumably, the bone marrow cells engrafted were sensitized by insulin preparations after bone marrow transplantation, resulting in insulin allergy in the patient. Moreover, allogeneic bone marrow transplantation is associated with modulation of T- and B-cell function, possibly causing the onset of allergic disease after bone marrow transplantation. In our patient, modulation of B- and T-cell function after bone marrow transplantation may have caused insulin allergy. Lampeter *et al.* reported that Type 1 diabetes mellitus was transmitted after bone marrow transplantation from a donor to a recipient [14]. The precise mechanism remains to be elucidated.

On the relationship between insulin allergy and graft-versus-host disease, there have been no reports in the literature. Chronic graft-versus-host disease was reported to have an impact on the development of allergy after bone marrow transplantation: Agosti *et al.* observed a lower rate of transfer of allergen-specific hypersensitivity in patients who had chronic graft-versus-host disease than in those who did not [11]. However, when it comes to allergic diseases such as chronic sinusitis, data are conflicting [15,16]. Thus, further studies will be needed to clarify this issue. In our case, we presume that graft-versus-host disease had little effect on the development of insulin allergy, because insulin allergy and graft-versus-host disease occurred independently: the patient developed insulin allergy 1 year after acute graft-versus-host disease and 4 years before chronic graft-versus-host disease was diagnosed.

The management of insulin allergy includes switch to alternative insulin, the use of antihistamines, local or systemic corticosteroid therapies and specific desensitization [1–3]. In our case, an immunosuppression therapy using corticosteroids presumably modified a clinical cause: cessation of corticosteroids aggravated insulin allergy. We assume that insulin allergy developed soon after bone marrow transplantation, but indications of insulin allergy were masked by the effect of corticosteroids. We continued insulin therapy using insulin aspart four times per day, as insulin aspart caused the least skin reaction. This may result in long-term desensitization for insulin allergy in our patient and the disappearance of the insulin allergy. The property that insulin aspart rapidly dissolves into monomers may help reduce immunogenicity, because insulin aggregates cause insulin allergy in the skin [17]. Moreover, insulin aspart is shown to be less immunogenic than other types of insulin in a transgenic mouse model [18]. In certain patients with insulin allergy, insulin aspart did not cause allergic reactions [19,20]; in contrast, in other patients it induced insulin allergy [6,21]. Presumably, the predisposition to develop insulin allergy varies from patient to patient, indicating the importance of searching for the most efficacious type of insulin preparations on an individual basis. Other treatment options for life-threatening generalized insulin allergy were:

continuous subcutaneous insulin infusion by insulin pumps [22], plasmapheresis or pancreas transplantation.

In summary, this is the first description of insulin allergy after bone marrow transplantation. Our case underscores the effects of bone marrow cells on IgE-mediated type I allergy for insulin.

Competing interests

Nothing to declare.

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