

CASE REPORT

Development of transplant-acquired multiple food allergies: a case series

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ABSTRACT

Organ transplantation is a life-saving procedure that is widely used in autoimmune diseases, malignancies and organ failures. However, it can bring many complications such as less known and newly described ones e.g. transplant-acquired food allergy (TAFA). Although the causes of TAFA have not been fully elucidated yet, different mechanisms are involved in the pathogenesis, especially the effects of the transplanted liver on the host immune system, and the characteristics of the host, especially drugs that are frequently used in pediatric transplant recipients, such as tacrolimus. In this case series, we present our 3 patients who underwent liver transplantation and developed transplant-acquired multiple food allergies 9–28 months later.

KEY WORDS

food allergy, transplantation, tacrolimus.

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INTRODUCTION

Organ transplantation is a life-saving procedure that is widely used in autoimmune diseases, malignancies and organ failures. However, it can bring many complications. Although some may occur acutely, some may occur in the long term and may be life threatening. Graft rejection, infections, bleeding, systemic complications after drug regimens, as well as less known and newly described complications such as transplant-acquired food allergy (TAFA) can be seen [1–4].

In this case series, we present our patients who underwent liver transplantation and developed transplant-acquired multiple food allergies 9–28 months later (Table 1).

CASE REPORT

CASE 1

A 3-year-old girl patient, who had liver transplantation from her father as a living donor at the age of 8 months due to biliary atresia, and who did not have a known food allergy before, presented to the pediatric allergy immunology outpatient clinic with complaints of swelling of the lips and redness of the face after eating chocolate. Specific IgE against hazelnut was found to be 13.4 kU/l. Specific IgE against chocolate was negative. Hazelnut was excluded from the diet and the patient was followed up. During the follow-up, it was learned that she had food-induced anaphylaxis with shortness of breath, widespread redness and swelling in the whole body 0.5 h after eating jelly beans and potato chips 2 weeks before, and similar symptoms occurred 2 days after this reaction, after eating stick crackers. When

the anamnesis was deepened (made more detailed), the family also stated that the patient had a cough that started after drinking milk for the last year, lasted for 0.5 h and went away on its own. In her laboratory examinations, the results were as follows: milk-specific IgE: 5.71 kU/l, β -lactoglobulin 14.60 kU/l, α -lactalbumin 5.53 kU/l, egg white-specific IgE: 4.75 kU/l, egg yolk-specific IgE: 2.74 kU/l and potato-specific IgE was 0.63 kU/l. (All serum specific IgE evaluations in this article were performed by the chemiluminescence immunoassay method.) A skin prick test was also performed 1 month after anaphylaxis. Skin prick testing showed that histamine was 5 mm, negative control (saline) 0 mm, cow's milk 6 mm and whole egg 3 mm. Prick to prick testing for egg white was 5 mm. Milk and eggs were also excluded from the patient's diet. The patient started to receive immunosuppressive therapy (prednisolone, tacrolimus) immediately after transplantation, and after 3 months of the graft rejection attack, the dose of prednisolone and tacrolimus was increased and everolimus was added to the treatment. She continued to use tacrolimus and everolimus all the time, although prednisolone was discontinued and restarted at intervals. Due to the development of multiple food allergies, everolimus treatment was terminated by the transplant center where she was followed up. Tacrolimus was continued at a low dose. The family was informed about TAFA. An adrenaline autoinjector report was issued to the patient. In the follow-up, while she was on a milk, egg, hazelnut elimination diet, the patient had allergic reactions in the form of swelling and redness on the body and face, about 0.5 h after eating tomatoes, potatoes and peanuts. Tomato-specific IgE was 1.64 kU/l, potato-specific IgE 0.63 kU/l, peanut – 1.36 kU/l, milk- and egg-specific IgE values increased

TABLE 1. Demographic characteristics of the cases

Parameter	Case 1	Case 2	Case 3
Gender	Female	Male	Male
Transplantation age	8 months	9 months	7 months
Medicines used due to transplant	Tacrolimus, everolimus, prednisolone	Tacrolimus, prednisolone	Tacrolimus, prednisolone
Allergy development age	36 months	18 months	16 months
Foods that cause allergic sensitization	Milk, eggs, nuts, potatoes, peanuts, tomatoes	Pistachios, tomatoes, persimmon	Chicken meat, potatoes
Developing allergic reactions	Anaphylaxis (urticaria, angioedema + respiratory symptoms)	Angioedema	Anaphylaxis (urticaria, angioedema + respiratory symptoms)
Adrenaline auto injector	Yes	No	Yes
Donor	Living donor/father	Living donor/father	Living donor/aunt
Known allergy history in the donor	Allergic rhinitis	No	No

TABLE 2. Allergen-specific IgE values (kU/l) of Case 1

	Hazel-nut	Peanut	Milk	Alpha lactalb.	Beta lactoglob.	Casein	Egg white	Yolk	Walnut	Wheat	Toma-toes	Potatoes	Choco-late
29.09.2021	13.4	< 0.1											< 0.1
11.03.2022	6.47	< 0.1	5.71	5.53	14.6		4.75	2.74	< 0.1	0.7			
18.07.2022	23.7	1.36	10.6	15.8	22.7	7.2	10.9	7.26			1.64	0.63	

despite diet (Table 2). In addition to milk, egg, hazelnut elimination diet, tomatoes, potatoes and peanuts were also excluded from the patient's diet. Our patient had multiple food allergies and she was sensitized probably to milk, eggs, and nuts in chocolate; milk and eggs in jelly beans and crackers. During the follow-up, we evaluated her tolerance to the sensitized foods with food challenge tests. She later successfully passed the food challenge tests with potatoes and eggs. Potatoes and eggs were added into her daily diet (elimination diet was stopped). The follow-up continues. (Informed consent was taken from parents of this child.)

CASE 2

A male patient with no known food allergy, who underwent liver transplantation from his father as a living donor at the age of 9 months due to progressive familial intrahepatic cholestasis (PFIC) type 2, presented to the emergency service at the age of 18 months because of swelling on the lip 30 min after eating egg-cheese mixture and pistachio paste for breakfast. Pheniramine and prednisolone were administered parenterally in the emergency department, and the child was referred to the allergy outpatient clinic. In the tests performed on the patient, egg white-specific IgE was 0.48 kU/l, and egg yolk-specific IgE was 0.40 kU/l. In the prick-to-prick skin test, a 2 × 2 mm reaction was observed against pistachio (negative: 0 mm, positive control: 4 mm). Eggs and pistachios were excluded from the patient's diet. Specific IgE values (walnut, casein, peanut, egg yolk, cow's milk, tomatoes, β-lactoglobulin, egg white, hazelnut, α-lactalbumin, egg, wheat, banana specific IgE) measured after 6 months were negative. The patient's diet was opened with a baked egg. During the follow-up, the patient had angioedema after eating tomatoes and persimmons. The family of the patient whose child was treated with tacrolimus and prednisolone as immunosuppressants was informed about TFA. On the other hand, since tacrolimus caused thrombocytopenia in the follow-up, the immunosuppressive treatment was changed to cyclosporine by the transplant center. The patient is being followed up. (Informed consent was taken from parents of this child.)

CASE 3

A male patient who had liver transplantation from his aunt as a living donor at the age of 7 months due to biliary atresia, without any known food allergies. When he was 16 months old, he touched a piece of raw potato to his mouth and threw it on the floor because he didn't like the taste. After 5–10 min, swelling started on his face and lips and he had shortness of breath. Subcutaneous adrenaline and pheniramine maleate were administered in the emergency department. The child was referred to the allergy clinic. An adrenaline autoinjector report of the patient was issued. The family of the patient whose child was receiving tacrolimus and prednisolone treatment was informed about TFA and its management. While under follow-up, lip swelling and saliva drooling occurred after eating ready-made cake bought from the market at the age of 2 years and 8 months, and chicken meat at the age of 3 years and 5 months. The family had administered the adrenaline autoinjector at home in both cases. Milk, egg, potato and chicken specific IgE values were negative. When the patient consumed cooked potatoes accidentally, there was no problem. He recently was able to consume the home-made cake. (Skin prick and oral provocation tests could not be performed due to the lack of cooperation of the patient and his family.) For chicken meat, the family did not accept the food challenge test. The 5-year-old patient is on a chicken meat elimination diet and is being followed up under control. (Informed consent was taken from parents of this child.)

DISCUSSION

Transplant-acquired food allergy identified in non-allergic transplant recipients was first reported in the 1980s. Bone marrow transplantation is seen as an allergic response to various foods that develops after solid organ transplantations such as kidney and liver. It has been reported in the literature that it is more common especially after liver transplantation. Acquired food allergy has a frequency of 10–17% in pediatric liver transplant patients treated with tacrolimus, and this rate is higher than the rate of food allergy in the population (8%) [4, 5]. In the reported cases, there are differences in the child's

previous history of allergic diseases (TAFAs) including age, transplant type, donor's allergic history, treatment regimen, family history of allergy, food allergy, and severity of allergy. The number and variety/type of allergenic substances that cause allergies are variable. Therefore, it is a clinical condition that is difficult to predict and prevent [6]. It was also seen in our patients after liver transplantation and developed against more than one food.

Although it was previously thought that TAFAs emerged after the transfer of the allergen gene with stem cells during bone marrow transplantation and the expression of the gene, TAFAs were observed in the donor after grafts taken from non-allergic donors, suggesting that different mechanisms are at play [7, 8]. Multiple mechanisms are thought to be involved in the etiopathogenesis of TAFAs, which is frequently seen after liver transplantation, such as development of a delayed type hypersensitivity reaction, the type of transplant, the age and general health of the recipient, the method of immunosuppression, and potentially the genetics of both the donor and the recipient [5, 9].

It is thought to be related to tacrolimus treatment, the calcineurin inhibitor, which is the most preferred drug, especially used in liver transplantation. Tacrolimus increases intestinal permeability and blocks the transcription of T cell growth factors such as IL-2. T cells transform into Th1 or Th2 after encountering the antigen. Th2 cells induce eosinophil (via IL-5) and IgE-mediated cytokines (IL-4, IL-13) that promote allergic inflammation, while Th1 cells secrete interferon γ (IFN- γ) and IL-13, which inhibit the action of IL-4. The balance between Th1 and Th2 cytokines is essential for the control of normal immune homeostasis. While impaired and allergic inflammation occurs with the response of Th2; Th1 is assumed to be protective against allergic disease. With the use of tacrolimus, the balance shifting in favor of Th2 facilitates the emergence of allergic diseases with the loss of control of IFN- γ /IL-4 production and synthesis of IgE antibodies [10]. It is known that tacrolimus can increase the immune responses of Th2 by triggering the production of IL-10. Tacrolimus also inhibits B-cell proliferation, preventing B-cell-mediated humoral alloreactivity in transplant patients. Its effect on T cell-dependent antibody production is uncertain [11]. Tacrolimus disrupts the intestinal barrier by inhibiting the cellular energy production of the intestinal mucosa. The risk of antigen uptake and food allergy may increase due to an impaired intestinal barrier and permeability. T-cell activation occurs in the liver by antigens migrating from the portal vein and begins to direct naive CD4⁺-T cells of liver-resident dendritic cells to Th2 differentiation. In all 3 of our patients, the development

of TAFAs seems to be related to the calcineurin inhibitor tacrolimus treatment besides host's and recipient's other cofactors.

The immaturity of the immune system and gastrointestinal system in some young children has been explained as some of these reasons [12]. In addition, the transplanted liver is a large and well-perfused organ rich in pluripotent hematopoietic stem cells and donor IgE antibodies that can alter the immunological response in the host. This suggests that it is associated with increased IgE-mediated sensitization and emergence of allergic disease [13]. In addition, delayed onset of food allergy may be thought to occur secondary to an increased exposure after limited exposure and an anergy to certain allergens due to diets specific to the previous disease, and increased exposure to the protein (allergen) in the diet after transplantation, especially in patients with chronic liver disease. In our patients, the use of a drug such as tacrolimus, as well as the realization of transplantation in infancy and, as it is said, the development of anergy can be considered to play a role in the development of TAFAs.

The time of emergence of TAFAs varies. As in our case, it can occur within months or within days. In three of our cases, clinical symptoms started 9–28 months after transplantation. TAFAs are generally defined with a higher rate (20%) in pediatric patients, and food allergy, especially anaphylaxis, in the infancy period is life threatening [14]. Literature data suggest that children with TAFAs typically have multiple food allergies. However, the number of patients reporting anaphylaxis is much lower. Therefore, the development of multiple food allergies and anaphylaxis in two of our cases is remarkable.

Our cases had liver transplantation in infancy and family awareness was low because there was no previous family history of atopy or different allergies. In accordance with the literature, food allergy has been seen in multiple forms [15]. In addition, having a history of anaphylaxis can be explained by the young age and the sensitivity of the immune system, and it is compatible with these reasons. No correlation could be found in the literature between the type of organ transplant and multiple food allergies [3, 6, 13].

Most patients who develop TAFAs have symptomatic relief, as our patients do, following reduced immunosuppression and an appropriately restricted diet [16]. Food allergy is usually thought to be observed temporarily, as seen in our case 2 having egg allergy.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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