

Food Allergy: Transfused and Transplanted

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Abstract The inadvertent transfer of food allergy from an allergic donor to an unsuspecting recipient by transfusion or organ donation is a relatively rare but intriguing event with potentially catastrophic consequences. Additionally, the development of food allergy in the recipient of a transplant from a donor who was not food allergic poses questions about why this occurs, why it is observed more frequently in some situations than others, and the mechanisms that may be involved. In this review, the transfer of food allergy by transfusion, bone marrow transplantation, and the transplantation of different solid organs is explored, and potential mechanisms in addition to the importance of careful monitoring are discussed.

Keywords Food allergy · Food hypersensitivity · Blood transfusion · Bone marrow transplant · Liver transplant · Organ transplant

Introduction

The transfusion of blood products is a safe, often life-saving therapy that is infrequently associated with adverse reactions. The field of bone marrow transplantation and solid organ transplantation has advanced to the point at which these procedures are routinely performed and will continue to increase in use as advances in the field improve outcomes. Although other complications occur more frequently, under certain circumstances, blood transfusions and organ trans-

plantations can render the recipient food allergic either transiently or, in some instances, permanently. This review discusses the potential for the development of food allergy in a transfusion or transplant recipient and the implications associated with this phenomenon.

Transfer by Transfusion

The passive transfer of allergy by blood transfusion was first reported by Ramirez [1] in 1919 and involved a nonatopic patient with aplastic anemia requiring regular blood transfusions who developed asthma while riding in a horse carriage in Central Park in New York. The reaction occurred soon after the patient had been transfused with the blood of a donor who Ramirez later discovered to be allergic to horse dander. Two years later, in 1921, the ability to passively transfer food allergy locally by intradermal injections of serum obtained from a food allergic donor was reported by Prausnitz and Küstner [2]. Oddly, Küstner was allergic to cooked, but not raw, fish. Aware of the report by Ramirez [1], Prausnitz, who was not fish allergic, decided to inject small aliquots of Küstner's serum intradermally into his own arm. The following day, injections of miniscule amounts of a boiled fish extract into the prepared sites on Prausnitz' arm resulted in positive skin tests, whereas similar injections into untreated skin did not, proving that a substance capable of transferring allergen sensitivity at least transiently could be found in the serum of allergic individuals. This technique is referred to as the Prausnitz-Küstner (P-K) test. In 1927, Walzer [3] demonstrated that ingestion of a culprit food could cause localized allergic reactions at skin sites of a non-food allergic individual who had been passively sensitized by the intradermal injection of serum from a donor allergic to the

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food. This not only reinforced that allergy could be passively transferred locally by a substance contained in the serum of an allergic donor but also proved that food proteins were absorbed from the gastrointestinal tract without being completely digested and circulated in the bloodstream in an immunogenic form. Further investigations on passive transfer by Walzer [3] and Coca and Grove [4] documented that reactions could be reproduced at sensitized sites by injection or ingestion of similar doses of allergen extract or food, respectively, over a period of about 6 weeks. This duration of sensitization is supported by a report in 1986, when Castells et al. [5] used P-K testing in the evaluation of a potato allergic patient by injecting her serum into the skin of a recipient who was not potato allergic. Initially, reactions occurred at the P-K sites within 10 min of potato ingestion and persisted for up to 5 h. During the next 7 weeks, the reactions gradually took longer to develop and decreased in intensity until day 60, when no reaction was noted following the ingestion of a potato-containing food. However, direct challenge of the sites with potato extracts still resulted in a cutaneous wheal and flare and even at 6 months after the passive transfer, the recipient reported itching at the P-K sites after potato ingestion. Relatively long sensitization times were also described in a 1941 report by Loveless [6] examining skin and mucosal reactivity to ragweed in recipients of blood transfusions from ragweed allergic donors. Skin test positivity to ragweed persisted for 7 weeks in one individual and for 20 weeks in another [6]. Thus, clinically relevant passive sensitization to a food or other allergen through transfusion of blood products from an allergic donor could reasonably be expected to last for several months.

The concerning clinical implications of these findings are validated by case reports of anaphylaxis attributed to passive transfer of food allergy by transfusion of blood or blood products. In 1976, a 63-year-old man with severe epistaxis experienced anaphylaxis 30 min after receiving a second unit of whole blood [7]. The blood donor was contacted and discovered to be severely allergic to fish with lesser sensitivity to beans and peas. Because no other cause could be identified and because the recipient had eaten fish twice in the 2 days before the transfusion, in addition to regularly ingesting beans and peas, passive sensitization by blood transfusion from the atopic donor was proposed as the cause. The passive transfer of nut allergy to a nonatopic recipient by the transfusion of fresh frozen plasma (FFP) from a peanut allergic donor was reported in 2007 by Arnold et al. [8]. Two days after being transfused with 2 U of leukocyte-depleted FFP, one of which was obtained from a 19-year-old woman with severe peanut allergy, an 80-year-old previously peanut tolerant woman experienced anaphylaxis within minutes of ingesting peanut butter. Two

weeks later, a skin prick test to peanut resulted in an 8-mm wheal, and her peanut-specific IgE level was 2.7 kU_A/L. Skin prick testing of the blood donor to peanut revealed a 5-mm wheal, and her peanut-specific IgE level was greater than 100 kU_A/L. Two months later, the recipient's skin prick test to peanut was negative, and peanut-specific IgE was undetectable in her serum. Three months after her reaction, she tolerated a supervised peanut challenge without symptoms. A fresh unit of whole blood was collected from the peanut allergic donor, and red blood cell, FFP, and platelet components were prepared by the same methods used by the blood collection agency. Peanut-specific IgE levels were measured in duplicate for each component, and the expected blood level in an average-sized recipient with a blood volume of 5 L following transfusion of each component was estimated. The predicted peanut-specific IgE level after transfusion calculated in this fashion was 56 kU_A/L for FFP, 21 kU_A/L for platelets, and 16 kU_A/L for red blood cells, suggesting that transfusion of each of these components into an average-sized recipient probably would result in clinically relevant sensitization that would likely last for several months.

Realizing the risk of passively sensitizing recipients to food and other allergens through transfusion prompted studies examining the prevalence of allergen-specific IgE antibodies among blood donors. In 1995, Stern et al. [9] investigated 477 consecutive blood donors in Sweden to ascertain the utility of a questionnaire in identifying potential donors who might be allergic to common food and inhalant allergens. Of the 359 (75.1%) donors who reported not being allergic, 12.3% had detectable allergen-specific IgE to food and inhalant allergens measured on serological examination. In 2005, Johansson et al. [10] performed a follow-up study to compare the prevalence of specific IgE antibodies to common food and inhalant allergens in Sweden and Norway and to see if there had been a change in Sweden during the years since the previous study. The ImmunoCAP (Phadia, Uppsala, Sweden) method was used to evaluate serum samples from 1,002 Swedish and 500 Norwegian donors for IgE antibodies to common food and inhalant allergens in addition to penicilloyl G and latex. More than 30% of the donors had IgE antibodies specific for at least one of the 14 allergens tested. Detectable IgE antibodies to foods were more common in Swedish (11.1%) than in Norwegian donors (2.2%). Although the food-specific IgE levels were usually relatively low, about 26% of the 2.3% of peanut-sensitized Swedish donors had high levels of peanut-specific IgE antibody, with four exhibiting levels between 20 and 50 kU_A/L. Thus, levels of food allergen-specific IgE encountered in selected potential donors could be high enough to render the recipient sensitive enough to experience an allergic reaction upon exposure to the culprit food.

Alternatively, the possibility of triggering an allergic reaction to a food by transfusing blood from a donor who recently ingested a food to which the recipient is allergic has been proposed [11]. At present, dietary restrictions are not imposed on donors prior to blood donation. The climbing incidence of peanut and tree nut allergy along with the continued popularity of foods containing nuts suggests that the risk of such reactions is increasing. In 1998, one tertiary care facility reported an overall transfusion reaction rate of 2.1% [12]. It is tempting to speculate that at least a small portion of these reactions could have been caused by the infusion of blood products containing a food allergen into a food allergic recipient.

Transfer by Bone Marrow Transplantation

The realization that food and inhalant allergies can be passively transferred transiently by transfusion raises the question of whether allogeneic hematopoietic cell transplantation could result in a more permanent transfer or, alternatively, a cure of allergic disease. An excellent review of this topic examining the available retrospective case reports and the only prospective study with prolonged follow-up in the literature [13, 14] was recently published by Khan et al. [15•]. They concluded that the transfer of allergic disease was convincingly demonstrated in four patients from retrospective studies, two of whom developed food allergy. Other cases were most often considered inconclusive due to a lack of information regarding the allergic status of the recipient before transplantation. One of the cases deemed conclusive was reported by Tucker and Barnetson [16] in 1986, describing a 9-year-old nonatopic boy with a normal serum IgE level who received a bone marrow transplant in July 1982 from his 7-year-old HLA identical brother for treatment of acute lymphoblastic leukemia. The donor was highly atopic, having developed atopic dermatitis at 4 months of age followed by asthma, allergic rhinitis, and food allergy to egg, fish, and baked beans by 1 year of age and peanuts by 4 years of age. In January 1983, the recipient first developed an allergic reaction after the ingestion of beans followed by subsequent allergic reactions to fish, banana, nuts, and egg. A significant increase in his total IgE level along with the development of food allergen-specific IgE on radioallergosorbent testing to foods was documented. Interestingly, he did not develop asthma, atopic dermatitis, or allergic rhinitis. The other convincing case was reported by Walker et al. [17] in 1986 and involved another 9-year-old previously nonatopic boy with acute lymphoblastic leukemia. He developed food allergy to beans, egg, and fish 6 months

after receiving a bone marrow transplant from his HLA identical younger brother, who had a history of similar food allergies in addition to atopic dermatitis, animal dander sensitivity, and asthma. Yet another case was reported by Bellou et al. [18] in 1997 and involved a 5-year-old boy with acute lymphoblastic leukemia without a previous history of atopy who received a bone marrow transplant from his HLA identical younger sister, who had a history of atopic dermatitis. His clinical course was complicated by acute graft-versus-host disease and cytomegalovirus infection. He developed severe atopic dermatitis within 6 months of the transplant, accompanied by significant sensitization to egg, peanut, and soybean. Eventual regression of his atopic dermatitis occurred upon strict avoidance of these foods. He had a positive oral challenge to egg at a 1-g dose. His sister was documented to have similar food sensitizations but to a lesser degree and at the time of the report tolerated egg ingestion without a reaction. These cases support the notion that food allergies can be passed from donor to recipient by bone marrow transfusion.

The documented transfer of food allergy by bone marrow transplantation begs the question of whether food allergy can be cured by bone marrow transplantation from a nonatopic donor to a food allergic recipient. Remission of latex allergy in one case [19] and atopic dermatitis in another [20] following bone marrow transplantation have been described, but to date, only one case of resolution of food allergy following bone marrow transplantation has been reported. In 2005, Hourihane et al. [21] described the case of a 12-year-old boy who developed atopic dermatitis at 6 weeks of age, followed by food allergies to peas and lentils by 1 year of age and peanut by 2 years of age. At 10 years of age, he underwent bone marrow transplantation from a healthy unrelated donor whose atopic status was unknown for treatment of an unclassified T- and B-cell deficiency. Although his eczema and other food allergies had resolved by 5 years of age, he was still considered peanut allergic at the time of transplant. His most recent peanut-specific IgE level prior to transplant was obtained when he was 7 years old and was 23.7 kU_A/L, with a total IgE level of 2,533 IU/mL. He was demonstrated to be 100% donor engrafted. At 17 months post-transplant, his total IgE had fallen to 40 IU/mL, and peanut-specific IgE was undetectable. Skin prick testing to peanut was negative, as was an oral peanut challenge performed 2 years post-transplant, when he had been off all immunosuppressive medications for 9 months, documenting the resolution of his peanut allergy. The importance of 100% engraftment of the recipient in this case was emphasized, as partial donor chimerism could result in the survival of sufficient numbers of recipient allergen-specific T and B cells to maintain a continued allergic response.

Association With Liver Transplantation

New-onset food allergy after solid organ transplantation has been most often described following liver transplantation. Several cases have been described in which an adult organ recipient became food allergic after receiving a liver from a donor allergic to the culprit food [22–24]. The first case of the transfer of symptomatic peanut allergy by organ transplantation was described by Legendre et al. [22] in 1997. The death of a 22-year-old man caused by an allergic reaction to peanut accidentally ingested in a Satay sauce was followed by donation of his liver and right kidney to a 35-year-old man and his left kidney and pancreas to a 27-year-old woman, neither of whom was informed of the cause of his death. The recipients were not peanut allergic prior to transplantation, but 3 months later, the male recipient of the liver and right kidney developed a rash and laryngeal edema after eating peanuts. The presence of peanut-specific IgE antibodies was documented in the newly peanut allergic recipient by skin testing and a positive basophil degranulation test at the time of the reaction and declined rapidly thereafter. Testing for peanut protein-specific lymphocyte proliferation in an attempt to document the presence of peanut-specific donor T cells was negative. Evidence of microchimerism was not found in his blood but was identified in his skin. He was advised to avoid peanuts permanently. Testing for the presence of peanut-specific IgE and for microchimerism was negative in the woman who received the donor pancreas and left kidney, and she continued to eat peanuts without symptoms. Although the reaction occurred within a time frame consistent with the passive transfer of peanut-specific IgE from the donor, the transfer of allergen-specific donor lymphocytes was proposed by the authors as the more probable cause, in part because of the evidence for microchimerism in the patient's skin. The transfer of allergy only to the patient who received the donor liver was speculated as resulting from the migration and engraftment of pluripotential hematopoietic stem cells and dendritic cells present in the donor's liver, but not his other organs. Other cases of the transfer of food allergy accompanying liver transplantation from a food allergic donor include the reports by Phan et al. [23] and Vagefi et al. [24]. In 2003, Phan et al. [23] described the case of a 60-year-old man transplanted with the liver of a 15-year-old boy who died of peanut anaphylaxis. The recipient developed anaphylaxis after eating cashews 25 days after the transplant and accidentally ate peanut 32 weeks post-transplant, resulting in another episode of anaphylaxis requiring self-administered epinephrine. The presence of allergen-specific IgE to peanut and cashew in the recipient was documented by skin testing performed at 6, 8, and 48 weeks after transplantation, with a decrease in the size of the

cashew skin test and a lesser reduction in the peanut skin test size. Microchimerism could not be documented in the blood or skin of the recipient. Recipients of the donor's kidneys and pancreas did not become peanut or cashew allergic. The reactions in this case were attributed to the passive transfer of donor food-specific IgE residing in the liver sinusoids and extravascular space because microchimerism was not identified, the donor was on immunosuppression that would have inhibited antibody production at the time of the first reaction, and his skin test responses were decreased at 48 weeks. The most recent similar case was reported by Vagefi et al. [24] and involved a 54-year-old man transplanted with the liver of a 24-year-old woman who died of anaphylaxis to an unknown allergen. On the eighth postoperative day, he experienced anaphylaxis after eating a nut-containing ice cream. Surprisingly, skin testing and radioallergosorbent testing to multiple allergens were negative immediately following and 3 weeks after his reaction, but a food challenge to walnut reproduced his symptoms and was accompanied by an elevated serum tryptase. Thus, the authors cautioned that a recipient's risk of reaction may not always be identified by skin testing or checking for the presence of circulating serum-specific IgE.

The more common scenario for the development of food allergy after liver transplantation involves young children who are on tacrolimus (FK-506) immunosuppression after receiving orthotopic liver transplants from nonallergic donors. In 1997, Lacaille et al. [25] first reported the development of milk allergy in a child with an atopic background who was treated with systemic FK-506 after liver transplantation. In 1999, Inui et al. [26] reported the development of fish allergy in two atopic children after liver transplantation while on FK-506 immunosuppression. In an abstract published in the same year, 11 of 64 pediatric liver transplant recipients were reported to have subsequently developed food allergy, suggesting that the potential for the development of food allergy in this population was substantial [27]. In 2001, Nowak-Wegrzyn et al. [28] reported new-onset food allergy in six children following liver transplantation from nonatopic donors while on FK-506 immunosuppression. In 2003, Lykavieris et al. [29] evaluated 121 children treated with FK-506 following orthotopic liver transplantation and identified 12 who developed new-onset food allergy. The onset of food allergy occurred at a mean of 28 months after the transplantation. Interestingly, switching from FK-506 to cyclosporine A (CsA) in eight of the children led to symptom resolution even after reintroduction of the suspected foods into the diet. In a more recent report, Frishmeyer-Guerrero et al. [30] presented the findings of a retrospective review of 25 children under their care who developed food allergy after solid organ transplantation while on tacrolimus treatment, with only 3 of them not

involving liver transplantation. The patients were young with a median age of transplantation of 8.7 months; the median time from transplantation to the first allergic reaction to a food was 6 months, with clinical reactions occurring to a median of 4.5 foods. Interestingly, 15 of the 25 patients had findings consistent with eosinophilic gastrointestinal disease on biopsy. During a median 2.4 years of follow-up in their clinic and 6.1 years of follow-up by phone, 22 of the patients were still on restricted diets. Fifty-two of the 163 foods initially avoided were successfully reintroduced, with 17 of the 25 children having been able to reintroduce at least one food to their diet. The tendency for the development of eosinophilic gastrointestinal disease in these patients has been reported by others [31, 32]. In the only prospective study to date, Ozbeck et al. [33•] observed 28 children with a mean age of 4.96 ± 0.76 years who underwent orthotopic liver transplantation from donors who were not food allergic. Six (21%) developed multiple food allergies, and all had been treated with tacrolimus. The mean age of the six who developed food allergies was younger than that of the others (10.2 months vs. 68.9 months; $P < 0.05$). All became allergic to milk and egg, and five became wheat allergic. The onset of food allergy occurred within 1 year of the transplant in five patients and at 20 months in the remaining patient. Prior to developing food allergy, four of the patients developed Epstein-Barr virus infection. Whereas mean total eosinophil counts were similar in both groups before, they were higher in the food allergic group at each time point when measured at 3, 6, and 12 months after transplantation. Total eosinophil counts and total IgE levels decreased during the 6–12 months after the patients were placed on an appropriate elimination diet. The concept that host factors such as age as well as maturity and atopic tendency of the immune system at the time of transplantation might be important is raised by these studies and further supported by the case report of a split liver graft in which a child with a history of eczema who was transplanted at 19 months of age with the left lobe of a liver developed food allergy, whereas a 35-year-old woman without a history of atopy who was transplanted with the right lobe of the same liver did not [34].

Association With Other Organ Transplants

Although it occurs more commonly after liver transplantation, the development of food allergy following transplantation of other solid organs has been documented occasionally. In 2004, Chehade et al. [35] reported the development of food allergy in two children who had undergone intestinal transplantation. One was a 10.5-year-old girl with intestinal pseudo-obstruction and no personal or family history of

atopic disease who underwent intestinal transplantation at 8.5 years of age because of progressive intestinal failure. She developed facial and tongue edema with pruritus upon peanut ingestion 4 months after receiving her transplant while being treated with tacrolimus and 5 mg of prednisone daily. She remained symptom free on a peanut elimination diet. The other patient was a 12.5-year-old girl with no previous personal or family history of atopy who underwent intestinal transplantation at 6.3 years of age for treatment of progressive intestinal failure. She developed edema of her tongue and pruritus after the ingestion of clam, mustard, egg, and pork that began 2 years after transplantation while she was on treatment with tacrolimus and prednisone, 2.5 mg every other day. Her sensitization to these foods was documented by skin testing and the detection of serum food-specific IgE by ImmunoCAP. In both patients, intestinal biopsy specimens revealed mild eosinophilic infiltrates accompanied by other histologic findings typical of mild rejection. The atopic history of the intestinal transplant donors in these two cases was not mentioned in the report, but the delay in the onset of symptoms suggests the development of food allergy in the host rather than the transfer of food allergy from the donor.

The only reported case of the transfer of food allergy following lung transplantation to date was described by Khalid et al. [36] in 2008. A 42-year-old woman with a history of sarcoidosis successfully received a bilateral lung transplant from a 12-year-old donor with asthma and peanut allergy who died from an allergic reaction following the ingestion of a peanut-containing food. The recipient had no history of food allergy and was unaware of the donor's history of peanut allergy. She experienced her first reaction to peanut 4 days postoperatively when she became short of breath following the ingestion of a chocolate bar that contained peanuts. She had three other significant respiratory reactions following peanut ingestion at 5 weeks, 4 months, and 7 months after transplant, two of which required hospitalization, before she attributed her episodes to peanut ingestion. Allergy evaluation soon thereafter revealed a large positive skin test to peanut, documenting the presence of peanut-specific IgE likely released from the donor lung. At follow-up 5 years after the transplant, she had a negative peanut skin test, and peanut-specific IgE was undetectable in her serum. An offer for a peanut challenge was declined. At 7 years post-transplant, her skin test to peanut was still negative. An oral peanut challenge under close medical supervision resulted in chest tightness accompanied by a 20% decline in her forced expiratory volume in 1 s to 0.87 L at 30 min following the ingestion of one peanut. Not surprisingly, her lung was the primary target organ in each of her reactions. The early reactions could be explained by the transfer and persistence of donor peanut-specific IgE present at transplantation or possibly

made by immunocompetent cells in the donor lung. However, her pulmonary response to peanut ingestion at 7 years post-transplant in the absence of a positive skin test or detectable serum peanut-specific IgE raises the question of continued peanut-specific IgE production localized to the lung. The recipients of other organs from the donor, including a kidney–pancreas recipient and the recipient of the other kidney, were contacted and had not experienced problems with peanut ingestion.

Proposed Mechanisms

The development of allergy to a specific food in the recipient of blood products from a donor allergic to the culprit food is easily explained by the passive transfer of food allergen–specific IgE. The reactions are most pronounced soon after the transfusion and gradually decrease in severity during the following few months until resolution. In patients receiving allogeneic bone marrow transplantation from a food allergic donor, the reactions are readily explained by the adoptive transfer of food allergen–specific B and T lymphocytes from the allergic donor to the naïve recipient. In contrast to the transient nature of allergen sensitization by blood transfusion, sensitization by allogeneic bone marrow transplantation is somewhat delayed in onset and longer lived or even permanent.

Identifying the mechanisms responsible for the development of food allergy in liver transplant recipients is more complex, as there are several different clinical scenarios. The less common scenario involves transplantation of the liver from a food allergic donor into a naïve recipient. In this situation, reactions occurring soon after transplantation could be explained by the retention of enough allergen-specific IgE in the large vascular pool in the sinusoids of the donated liver to sensitize the recipient's mast cells. As previously mentioned, although IgE circulates in the peripheral blood for only a few days, it remains bound to high-affinity receptors on circulating basophils and tissue mast cells for several months. Alternatively, activation of mast cells in the donor's liver could lead to localized symptoms or result in sufficient mediator release to cause systemic symptoms. Longer-lived sensitization could also occur because the liver, as an immunologically privileged organ, contains not only donor T and B lymphocytes but also pluripotential hematopoietic stem cells and dendritic cells capable of surviving for several months and producing allergen-specific IgE. The migration of these cells into recipient lymphoid organs or other sites and provoking sensitization has been postulated based on evidence for microchimerism in at least one case [22].

Determining the mechanisms involved when the liver donor is not food allergic and the recipient develops food

allergy is more complicated. Dendritic cells and sinusoidal endothelial cells in the liver may participate in T-cell activation to food allergens circulating through the portal vein by preferentially directing naïve CD4⁺ T cells toward T-helper type 2 differentiation. Studies in a murine model suggest a unique role for the liver as the site of the development of helper CD4⁺ T cells for an IgE response to dietary antigens in a genetically susceptible host [37]. In addition, the development of food allergy in liver transplant recipients likely also depends on a combination of recipient factors, including—but not limited to—the family and personal history of allergic disease, age, maturation of the immune system, post-transplant infections, and the immunosuppression regimen used to prevent graft rejection. Notably, the shared features of the commonly reported cases are that they involve young children, most with a family or personal history of atopic disease, receiving liver transplants from nonallergic donors and treated primarily or secondarily with tacrolimus (FK-506).

Tacrolimus has been considered a significant risk factor due to several of its unique characteristics and because the symptoms of food allergy have resolved in some patients when they were switched from tacrolimus to another immunosuppressive agent, such as CsA. Tacrolimus and CsA have a similar mechanism of action involving inhibition of calcineurin, a protein phosphatase required for the translocation of an activation factor (NF-ATc) from the cytosol to the nucleus, where it binds to and activates enhancers and promoters of genes that control the production of interleukin-2 and other early activation factors. This inhibition causes repression of an early step of T-cell activation, thereby modulating T-cell cytokine production in addition to T- and B-cell activation and differentiation [38]. For example, tacrolimus, while inhibiting the production of interleukin-2 and interferon- γ , augments the production of interleukin-5 and interleukin-13, leading to skewing toward a T-helper type 2 response. Although they share a similar mechanism of action, tacrolimus has been shown to be 100 times more potent than CsA, which likely explains the resolution of food allergy in some patients when they are switched to CsA. Poor penetration through the skin, resulting in insignificant serum levels of the drug, likely explains why new-onset food allergy is not increased in patients with atopic dermatitis treated with topical tacrolimus [39]. The predominance of food allergies rather than the development of other allergies in transplant patients treated with tacrolimus has been attributed to its unique effect on the gastrointestinal mucosa, resulting in increased intestinal permeability [40]. Thus, it appears that young children with immature immune systems and a predisposition to allergic disease, when treated with tacrolimus, which can increase intestinal permeability and tilt the immune system toward a T-helper type 2 response,

are at highest risk for the development of new-onset food allergy following liver transplantation. The importance of the transplanted liver in the development of food allergy is emphasized by the paucity of new-onset food allergy observed in other solid organ transplants and is likely due to the previously mentioned immunoprivileged aspects of this organ. Other insights regarding the basic mechanisms for the development of food allergy likely would be gained from further study of these patients.

The possibility of persistent production of IgE confined to the transplanted organ is suggested by the case involving the recipient of a lung transplant from a peanut allergic donor [36] and the case of the adult who reacted to walnut after receiving a liver transplant from a nut allergic donor [24]. The reactions occurring in these patients in the absence of positive skin tests or the ability to identify serum food allergen-specific IgE near the time of the reaction reinforce the need for caution in the evaluation of these patients.

Conclusions

The potential for the transfer or development of new food allergy following transfusion or transplantation emphasizes the need for closer monitoring of these procedures at several different stages of the process. The allergic status of the donor should be ascertained and shared with the potential recipient. When necessary, the recipient should be educated regarding avoidance of the suspected allergen and the treatment of reactions resulting from accidental exposure, including how to use an auto-injectable epinephrine-containing device. The recipient's family history of allergic disease should be recorded and any personal history of allergic disease investigated prior to transplantation, particularly in recipients likely to receive tacrolimus. After transplantation, monitoring peripheral eosinophil counts and total IgE levels in combination with skin testing and serial measurement of serum food allergen-specific IgE levels as indicated by the history seems warranted. Longitudinal follow-up, including cautious reintroduction of the suspected food to the diet under medical supervision when the history, skin testing, and measurement of serum food allergen-specific IgE suggest it would be safe, is indicated. We hope that by increasing awareness of the potential for these reactions and with increased monitoring, their frequency, or at least the morbidity associated with them, can be significantly reduced.

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