



Case report

Transfer of peanut allergy from donor to recipient after liver transplant

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ABSTRACT

31 years old female with a history of contact dermatitis, eczema, allergic rhinitis, pernicious anemia, alopecia areata and latent tuberculosis was treated concurrently with methotrexate along with isoniazid and pyridoxine. Five months into the therapy she developed acute onset jaundice progressing into fulminant liver failure with altered mentation and worsening liver function tests. Extensive workup including serological and histopathological evaluation revealed drug-induced liver injury as the etiology of her liver failure and she underwent a successful orthotopic liver transplant. On post-transplant follow-up at four months, she was noted to have an allergic reaction consisting of a perioral rash and swelling (without anaphylaxis) after receiving a kiss from her significant other who had just eaten a peanut butter chocolate. She denied any history of allergic reaction to peanuts prior to the transplant. Percutaneous skin testing revealed immediate hypersensitivity to peanut, hazelnut, and pecan believed to be acquired newly post-transplant. Further investigation revealed that the organ donor had a documented history of systemic anaphylaxis from the peanut allergy and a positive peanut-specific IgE level. Also, another parallel solid organ recipient (lung transplant) from the same organ donor experienced a serious anaphylactic reaction after peanut exposure. This is a case of food (peanut) allergy transfer from the donor to the recipient after the liver transplant. This case highlights the importance of incorporating known donor allergies as a part of pre-transplant screening, given the potentially serious consequences from the transfer of allergies to a previously anergic recipient.

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1. Case

31 years old female with a history of shingles, eczema, contact dermatitis, allergic rhinitis, and pernicious anemia (requiring temporary vitamin B12 injections) presented to her primary care physician with patchy hair loss. She was evaluated by dermatology and diagnosed with alopecia areata. After worsening hair loss and failure of localized intradermal Interleukin 10 injections, she was initiated on methotrexate and tapering doses of prednisone. During her pre-methotrexate evaluation, she was found to have latent tuberculosis and concurrently treated with isoniazid/pyridoxine by the infectious disease team. Five months into her combined therapy (methotrexate/isoniazid/prednisone), she presented to her

primary care physician with scleral icterus, jaundice, and abdominal discomfort. Laboratory investigation at that time revealed liver function tests with elevated aspartate aminotransferase (AST) of 1665 IU/L, alanine aminotransferase (ALT) of 1419 IU/L, and total bilirubin (T. bili) of 6.7 mg/dl. She was sent home with close lab monitoring but was brought to the emergency room by her family 2 weeks later due to altered mentation and worsening jaundice. Her repeat liver panel tests were notable for AST of 1492 IU/L, ALT of 1990 IU/L, T. bili of 36.3 mg/dl, and her coagulation panel was notable for elevated prothrombin time (PT) of 53.1 (seconds) and international normalized ratio (INR) of 5.7. She was thought to have acute hepatic encephalopathy in the setting of acute fulminant liver failure. Hospital workup and biopsy was consistent with

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drug induced liver failure and she underwent successful emergent orthotopic liver transplant two days after presentation.

Post-transplant, she tolerated the immunosuppressant therapy well and her liver function tests and coagulation tests normalized. Her initial immunosuppression regimen included tacrolimus, mycophenolate mofetil and prednisone (10 mg daily), however mycophenolate was later discontinued due to leucopenia and upper respiratory infection. Four months post-transplant, she was noted to have an immediate allergic reaction consisting of a perioral rash and swelling (without anaphylaxis) after receiving a kiss from her significant other who had just eaten a peanut butter chocolate. She denied any history of allergic reaction to peanuts or other nuts prior to transplant. She was referred to an allergist and was found to have developed immediate hypersensitivity to peanut, hazel nut, and pecan on percutaneous skin testing (Table 1). Serologic testing was negative for total IgE (normal, <1 IU/ml), peanut specific allergen and recombinant allergens (<0.1 kU/L). Further investigation revealed that the organ donor had a documented history of systemic anaphylaxis from peanut allergy with a peanut specific IgE level of 9.74 kU/L and peanut component testing showing positive IgE to Ara h 1, 2, 8 and 9. In addition, previously anergic parallel patient who had received lung transplant from the same donor experienced a serious allergic anaphylactic reaction after exposure to peanuts a few months post-transplant.

Two months after the acquired peanut allergy from liver transplant, the patient followed up in allergy clinic. Skin testing was repeated during that visit and showed negative results for peanut allergies. She subsequently underwent monitored oral food challenge with a peanut butter cup which led to minimal symptoms of lip tingling without developing a rash or an overt hypersensitivity reaction. There was no change in her immunosuppression throughout this period and around the time of repeat allergy testing.

2. Discussion

This is a case of post-transplantation antigen sensitization in a patient with previous anergy to specific antigens like peanuts, hazel nuts, and pecans.

The development of *de novo* food allergies in transplant recipients has been described after solid organ transplants predominantly in pediatric populations with frequencies ranging from 5% to 38% [1–4]. Furthermore, immunosuppression with tacrolimus was found to be associated with the development of allergies. This effect was also seen primarily in pediatric populations but the type of organ transplanted was also implicated as a risk factor. Interestingly, multiple studies showed that in patients transplanted at a younger age, the development of allergies are much more common in recipients of liver transplants compared to kidney transplants [1,2,5]. Bone marrow, liver and small bowel transplants result in transplantation of hematopoietic lymphoid tissue and are thus affiliated with allergen sensitization [6]. Multiple factors that have been

implicated in the process of acquiring new allergies post-transplant are summarized in Table 2 [7].

Although exact or defining central pathways are yet to be elucidated, various suggested mechanisms and associated factors that lead to post transplantation presentation of food allergy have been postulated as below (5) [7]:

1. Passive transfer of donor IgE. IgE has a short half-life ranging from a few days in serum to a few weeks on the surface of tissue resident mast cells [8].
2. Transfer of allergen specific T- and/or B-lymphocytes, leading to active production of specific IgE for months after transplantation [9,10]. This results in ongoing cellular and humoral immune response to the allergen.
3. Presence of an immature immune-regulatory response in transplant recipients that fail to suppress the expression of new acquired food allergies [11].

Transfer of allergen-specific IgE mediated hypersensitivity after allogeneic bone marrow transplant has been well recognized [12] and a substantial proportion of patients may maintain hypersensitivity past one year. Liver homes pluripotent hematopoietic stem cells which are capable of generating allergen-specific lymphocytes upon transfer to recipient [13]. These carrier lymphocytes can persist for months in the recipient causing delayed food allergy onset in transplant recipients [3]. To detect donor-origin cells in the recipient, DNA extraction and amplification for HLA genotype micro-chimerism testing has been done in the blood and skin of transplant recipients. However, cases have been reported with both

Table 2
Factors implicated in transplant-acquired food allergy.

Factors		Possible mechanism
Transplant organ	Liver > kidney	1. Transplanted liver has hematopoietic stem cells 2. Larger organ size and vascularity causing higher probability of transferring sensitized lymphocytes 3. Clinical expression of already present allergy due to correction of immune dysfunction after the transplant 4. Transfer of dendritic and sinusoidal endothelial cells can promote IgE response to an antigen
Type of immunosuppression [14]	Tacrolimus > other immunosuppressants	1. T-helper cell (Th1 and Th2) imbalance promoting IgE production 2. Tacrolimus is more potent in enhancing IgE production and eosinophil-associated Th2 cytokines (IL-5, IL-13) 3. Tacrolimus can increase intestinal permeability and can possibly promote systemic allergen exposure 4. Mycophenolate can be protective as it suppresses B-lymphocytes and hence reduces IgE production
Recipient-specific factors	Age of recipient (younger/children > adults) Family history of atopy	Presence of immature immune-regulatory response Possible pre-existing genetic predisposition
Donor-specific factors	Personal history of atopy	

Table 1
Skin prick testing results.

Allergen	Skin wheal size (mm)	
	At diagnosis	2 months after
Isotonic saline (control)	0	0
Histamine (control)	4	4
Peanut	4	0
Hazel nut	4	n/a
Pecan	4	n/a
Egg white	0	n/a
Soybean	0	n/a
Cashew	0	n/a
Pistachio	0	n/a
Almond	0	n/a

Table 3
Summary of Liver Transplant Acquired Food Allergy Cases.

Case/series	No. of patients Allergy/total	Organ	Demographics (age, sex)	Allergy	Time to symptom onset	Immunosuppression	Test	Outcome
Berry et al. [15]	1/1	Pancreas–kidney combined	32 year old female	Peanut	1 month	Unknown	Skin test, IgE levels	Transient with resolution at 6 months
De Bruyne et al. [17]	13/49	Liver	Age (2–48 months) 29 males/20 females	Cow milk, eggs, peanut, soy	1–48 months	Tacrolimus, MMF, Cyclosporine, Sirolimus	Skin test, IgE levels	1 in 13 outgrew allergy. Follow up 33–188 months
Topal et al. [18]	6/165	Liver	2 adults, 4 children 114 males/51 females	Eggs, milk, banana, lentils	2–36 months	Tacrolimus, MMF, Cyclosporine	Skin test, IgE levels	Unknown, retrospective study
Lee et al. [4]	35/93	Liver	Age (11–20 months) 36 males/57 females	Eggs, milk, soybean	2–10 months	Tacrolimus	IgE levels	29 had improvement in food allergies by 1 year follow up
Ozbek et al. [19]	6/49	Liver	Age (8 months to 17 years) 1 male/5 females (allergy) 23 males/26 females	Eggs, milk, peanut, banana, potato	1–14 months	Tacrolimus	IgE levels	Unknown
Catal et al. [20]	6/28	Liver	Age (6–16 months) 4 male/2 females (allergy)	Eggs, milk, lentil, wheat, peach	3–20 months	Tacrolimus	Skin test, IgE levels	4 in 6 outgrew allergy. Follow up 7–38 months
Shroff et al. [2]	10/176	Liver	Age (median 11.5 months)	Eggs, peanut, milk	4–135 months	Tacrolimus, Cyclosporine	IgE levels	Unknown, no follow up eval noted
Levy et al. [21]	4/65	2 liver and 2 liver/kidney	Age (1–7 yo) 2 males/2 females	Eggs, milk, soybean, fish, nuts	1–6 years	Tacrolimus, MMF, Cyclosporine	IgE levels	All resolved in the setting of allergen avoidance
Marcus et al. [1]	17/111	Liver	Age (9–83 months) 63 males/48 females	Not disclosed in series	7 months median, 14 months mean	Tacrolimus	Skin test, IgE levels	Unclear given food allergy data combined with other post-transplant allergies
Narumoto et al. (2018) [22]	1/1	Liver	10 month old female	Milk	5 days	Tacrolimus, Cyclosporine	Diarrhea, enteritis, surgery	Resolved in the setting of allergen avoidance
Lebel et al. [23]	12/154	Liver	Age (1–24 months) 5 males/7 females	Eggs, legumes, milk, peanut, tree nut, sea food	6–95 months	Tacrolimus, Cyclosporine	Skin test, IgE levels	Unknown, no follow up eval noted. 17% of patients with tacrolimus had food allergy vs 3% with cyclosporine
Noble et al. [24]	12/60	Liver	Age (0.1–11 years) 8 males/4 females	Eggs, wheat, soy, sea food, dairy	2–59 months	Tacrolimus	Skin test, anaphylaxis	Unknown given loss to follow up
Ozdemir et al. [25]	1/1	Liver	18 month old male	Eggs, peanut	7 months	Tacrolimus	IgE levels, ImmunoCAP test	Resolved in the setting of allergen avoidance
Phan et al. [8]	1/1	Liver	60 year old male	Tree nut, peanut	0.8 months	Tacrolimus, Azathioprine	Skin test, IgE levels	Persistent at 48 months follow up

Table 3 (Continued)

Case/series	No. of patients Allergy/total	Organ	Demographics (age, sex)	Allergy	Time to symptom onset	Immunosuppression	Test	Outcome
Vagefi et al. [26]	1/1	Liver	54 year old male	Tree nut	8 days	Tacrolimus, MMF	Anaphylaxis, skin test, IgE levels	Transient with resolution at 12 months
Pacifico et al. [27]	1/1	Liver	6 month old female	Milk	2 months	Tacrolimus	Skin test, IgE levels	Resolved in the setting of allergen avoidance
Trotter et al. [28]	1/1	Liver	28 year old female	Peanut	0.3 months	Cyclosporine	Skin test, IgE levels	Unknown
Dewachter et al. [6]	1/1	Liver	62 year old female	Peanut	2 months	MMF, Cyclosporine	Anaphylaxis, skin test, IgE levels	Transient with resolution of specific IgE at 3 months and skin test at 6 months
Lacaille et al. [29]	1/1	Liver	7 month old	Milk	5 months	Tacrolimus	Unknown	Unknown
Inui et al. [30]	2/2	Liver	Age (2.5–3 years) 2 females	Sea food	3–29 months	Tacrolimus	IgE levels	Resolved in the setting of allergen avoidance
Lykavieris et al. [31]	12/121	Liver	Age (6–36 months) 7 males/5 females	Eggs, soy, wheat, milk, peanut, tree nut, sea food	13–45 months	Tacrolimus	Angioedema, IgE levels	Transient in 8 children at 2.5 yrs after Tacrolimus switched to Cyclosporine
Ozbek et al. [32]	6/28	Liver	Age (6–16 months) 4 males/2 females	Eggs, wheat, milk	3–20 months	Tacrolimus, Cyclosporine, Rapamycin	IgE levels	Resolved in the setting of allergen avoidance
Boyle et al. [11]	1/1	Liver	19 month old male	Eggs, peanut	1 month	Tacrolimus, Azathioprine	Skin test, IgE levels	Unknown although second recipient of same liver did not have any atopy to eggs or nuts
Arikan et al. [33]	3/50	Liver	Age (5–13 years), no sex reported	Eggs, peanut	4–9 months	Tacrolimus, Cyclosporine	IgE levels	Resolved in the setting of allergen avoidance
Saeed et al. [34]	3/45	Liver	Age (1.5–7 years) 2 males	Eggs, wheat, milk	17–24 months	Tacrolimus	IgE levels	Complete resolution of symptoms in 1 and partial resolution with allergen avoidance in 2
Cardet et al. [35]	1/1	Liver	5 month old female	Eggs, soy, peanut, wheat	9 months	Cyclosporine, Tacrolimus, MMF	Skin test, IgE levels	Improvement in food allergy and gastrointestinal symptoms after switch to MMF from tacrolimus
Mavroudi et al. [36]	3/3	Liver	Age (6–8 months) 1 males/2 females	Eggs, sesame, milk, sea food	12–186 months	Tacrolimus, Azathioprine	Skin test, IgE levels	Complete resolution of symptoms in 1 (boy) and partial resolution with allergen avoidance in 2
Legendre et al. [9]	1/1	Liver/kidney	35 year old male	Peanut	3 months	(OKT3), azathioprine, cyclosporine	IgE levels	Resolved in the setting of allergen avoidance

detection [9] as well as absence [8] of such micro-chimerism in the recipient skin or blood, thereby highlighting the multi-pathway mechanisms for such allergy transfer. Another case reported a circulating population of donor-derived CD86+ memory T cells in the recipient that could contribute to maintaining the allergen-specific IgE response [14]. The mechanisms involving the transfer of allergen-specific immunoglobulins and lymphocytes would not explain the development of food allergy in transplant recipients where the donors did not have a confirmed similar food allergy [11].

Due to the small number of reported cases of food allergy transfer after solid organ transplant in adults, it is unclear whether the effect is temporary or permanent [6,8,9]. Most of the cases and patient series have been reported in pediatric population and have been summarized in Table 3. In a report by Berry et al. [15], a patient was followed up with serial serum IgE and skin prick testing to show normalization of these biomarkers at 6 months suggesting allergen sensitization in some patients is a transient phenomenon. Similarly, in our patient, the skin patch testing results became negative over 3 months followed by successful oral peanut challenge. For these cases, given the rapid loss of sensitization in these patients, passive transfer of donor IgE is the most likely mechanism of food allergy transfer. Also of note is the possible relation of rash development to mycophenolate discontinuation, which can be protective (Table 2).

In summary, although organ recipients and donors undergo a comprehensive pre-transplantation screening, allergy testing is not incorporated as a standard item. Given the potentially serious consequences of allergy transfer post-transplant, careful screening of the donor to including history of food and non-food allergies, when possible, could help identify transplant recipients at risk of experiencing post-transplant anaphylaxis. The ease of an allergy screen makes it a useful tool as we strive for positive outcomes and good organ stewardship post transplantation.

Abbreviations

IgE	immunoglobulin E
AST	aspartate aminotransferase
ALT	alanine aminotransferase
T. bili	total bilirubin

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Conflict of interest

No conflict of interest exists.

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