

Case Report

De Novo Food Allergy After Intestinal Transplantation: A Report of Three Cases

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Intestinal transplantation is increasingly performed to treat conditions once uniformly fatal. The de novo development of food allergies has been described after liver and bone marrow transplantation (1–5), but at our center, we have observed severe food allergy developing de novo after intestinal transplantation. Between 1999 and 2001, 28 pediatric patients at the Mount Sinai Medical Center underwent intestinal or combined intestinal-liver transplantation. We report three patients who experienced food allergy after their intestinal transplantation. Two patients had undergone transplantation at our center, and one patient had undergone transplantation at another center.

CASE REPORT

Patient 1

Patient 1 is a 10.5-year-old girl with intestinal pseudo-obstruction, who, from the age of 3 years, ate a regular diet, including peanuts, without problems. She had no personal or family history of food allergy or atopy. She underwent intestinal transplantation at 8.5 years for progressive intestinal failure. Four months after the transplantation, while she was receiving a regular enteral diet, she experienced facial and tongue edema with pruritus after eating a peanut butter sandwich. She had no associated emesis or diarrhea. Her symptoms resolved spontaneously after 1 hour. Subsequently, the same symptoms recurred after eating a cookie containing peanuts. She was able to tolerate other highly allergenic foods,

such as fish and tree nuts. She was receiving tacrolimus and low-dose prednisone (5 mg daily) for immunosuppression. Her peripheral eosinophil count was 546 cells/mm³ (normal, 30–700 cells/mm³). Her intestinal biopsy specimens showed eosinophilic infiltration on one occasion, but this finding was accompanied by other typical histologic features of rejection. Her symptoms have not recurred since she has avoided peanuts.

Patient 2

Patient 2 is a 12.5-year-old girl with intestinal pseudo-obstruction. Before undergoing transplantation, she was exposed to a regular diet and had no personal or family history of food allergy or atopy. At age 6.3 years, she underwent intestinal transplantation for progressive intestinal failure at another center and is now followed up at our center. Two years after the transplantation, she experienced tongue edema and pruritus after ingestion of clam, mustard, egg, and pork. She required diphenhydramine and prednisone to treat the symptoms. She had no emesis or diarrhea. The diagnosis of food allergies was confirmed by positive prick skin testing and elevated serum food-specific IgE antibodies (kIU/L, CAP System FEIA, Pharmacia Diagnostics, Uppsala, Sweden): clam 39.7; mustard 9.2; egg white 31.5; and pork 43.6. Other food antibodies were elevated. Her IgE antibody to beef was 21.4; blue mussel 3.6; chicken 2.9; codfish 13.4; crab 0.4; lobster 3.3; milk 3.1; salmon 12.6; shrimp 15.8; tuna 14.1; turkey 48.3; banana 5.9; soybean 5.9; almond 2.9; Brazil nut 7.0; cashew nut 23.7; hazelnut 16.3; peanut 3.3; and sesame seed 10.3. She was receiving tacrolimus at a dose sufficient to keep trough blood levels between 4 and 5 µg/L and low-dose prednisone (2.5 mg every other day). Her peripheral eosinophil count was 0 cells/mm³. Her intestinal biopsy specimens showed mild intestinal eosinophilic infiltrate on two separate occasions but with additional features typical of rejection. Her symptoms have not recurred since she has avoided the four offending foods.

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Patient 3

Patient 3 is a 3.5-year-old boy with severe cholestasis and short bowel syndrome caused by intestinal malrotation and volvulus. His diet before transplantation was restricted to an amino-acid based enteral formula. He had no personal history of atopy, but his father reportedly had childhood asthma. The patient underwent combined liver and intestinal transplantation at the age of 2 years. Eight months after transplantation, he experienced facial edema, hives, and vomiting after ingestion of milk and eggs, which was treated with epinephrine. He received maintenance doses of tacrolimus that kept the trough blood levels between 15 and 20 $\mu\text{g/L}$ and also took prednisone (7 mg by mouth daily) but had not received any large steroid boluses. He had a severe Rotavirus enteritis before experiencing the food-allergic reaction. Serum levels of specific IgE antibodies directed against milk and eggs were significantly elevated (kIU/L, CAP System FEIA, Pharmacia Diagnostics, Uppsala, Sweden): milk 38.1; and egg white 53.5. He also had IgE antibodies to other foods: beef 3.5; chicken 1.7; apple 0.4; soybean 8.6; wheat 14.1; almond 1.1; and peanut 7.2. He had no peripheral eosinophilia (132 cells/ mm^3) but had gastrointestinal mucosal biopsy specimens showing eosinophilic esophagitis and ileitis after an oral milk challenge 11 months later (undertaken without the approval of his physicians). His symptoms have not recurred since he has strictly avoided milk and eggs.

DISCUSSION

We report three patients who experienced *de novo* food allergies at various times after intestinal transplantation. All three had immediate IgE antibody-mediated symptoms. Underlining the potential seriousness of the phenomenon, one patient required treatment with epinephrine. We think these patients experienced food allergies as a result of transplantation. Food allergy has a peak prevalence of 6% to 8% in infants and young children, with a gradual decline to 1% to 2% in adulthood (6). Although there are no published studies on the onset of food allergy at different ages, many studies indicate that milk and egg allergy resolve in 85% of affected children by the age of 5 years (7). We cannot exclude the possibility that the allergic reaction of patient 3 was destined to develop unrelated to his transplantation. He was within the age that food allergy might be expected to appear; he had no history of tolerance to food allergens before transplant; and he had a paternal history of atopy.

Two theories have been advanced to explain food allergy as a consequence of transplantation. The first theory implicates suppression of type 1 helper T lymphocytes (Th1) by immunosuppressants such as cyclosporine or tacrolimus, which are interleukin-2 inhibitors (8). This selective suppression might promote a type 2

helper T-lymphocyte (Th-2) population, which in turn might promote immediate allergic responses (3,4). The second theory is that the transplanted organ transfers atopy from donor to recipient via donor lymphocytes or mast cells contained in the transplanted organ (1,2,5,9).

Bellou et al. (1) reported a 5-year-old boy with no history of atopy who experienced severe atopic dermatitis after bone marrow transplantation from his 2.5-year-old sister who had atopic dermatitis and possible allergy to cow's milk protein during her infancy. A study of bone marrow chimerism in the patient showed that all cells were XX (donor type). This finding would support the hypothesis of transfer of atopy. However, the hypersensitivity was more severe in the recipient than in the donor, which suggests an additional role of the post-transplant immunosuppression (cyclosporine in this case) in creating a predominant Th-2 lymphocyte population.

Additional support for the idea of helper T-lymphocyte imbalance is provided by a report on three children who experienced symptomatic eosinophilic gastroenteritis after liver transplantation. These patients were receiving cyclosporin A, and all received large boluses of steroids without taper before experiencing gastrointestinal symptoms. Steroids in large doses could have had a general lympholytic effect that promoted the Th-2 responsiveness of the children, which in turn may have promoted eosinophilia (10). Our patients did not have sustained gastrointestinal symptoms with their immediate allergic reactions, although one patient experienced intestinal tissue eosinophilia after exposure to the food allergen. The other two patients had mild eosinophilia in the presence of other features suggesting rejection, so eosinophilia might have represented rejection, rather than an allergic process. None of the patients had peripheral blood eosinophilia; however, peripheral blood eosinophilia is not a very sensitive marker of tissue eosinophilia. For example, it is present in only 50% of cases of eosinophilic gastroenteritis (11). In two patients, IgE antibodies to multiple foods were present, including foods that patients could eat without obvious reactions. Although the clinical significance of these food IgE antibodies is not clear, we suspect that they might be a reflection of the Th-2 predominant environment, which would be characterized by increased secretion of interleukin-4 and interleukin-13, cytokines that promote immunoglobulin class switching toward IgE. In contrast to the report by Dhawan et al. (10), the allergic reactions in all of our patients did not occur after a large steroid bolus or during a steroid taper.

The theory of transfer of atopy is supported by a report by Legendre et al (2), in which an organ donor who had died as a result of an anaphylactic reaction to peanut appeared to pass the allergy to a recipient of his liver and right kidney, but not to the recipient of his left kidney and pancreas. Both recipients received tacrolimus as primary immunosuppression. Testing for microchimerism

revealed its presence in the recipient who experienced peanut allergy but not in the other, which supports the theory of transfer of allergy. In our cases, we could not test for microchimerism, and the food allergy status of their donors was unknown. However, the organ donor for patient 1 was known to have asthma and died during an episode of status asthmaticus.

Another possible explanation for the development of food allergy could be increased intestinal permeability after intestinal transplantation, which could increase the amount of antigenic exposure and whole protein absorption, thereby increasing the likelihood of allergic reactions. Several factors may increase intestinal permeability after intestinal transplantation. In one report, tacrolimus was found to increase intestinal permeability after liver transplant as measured by the lactulose/L-rhamnose absorption test (12). It is not clear whether the higher dose of tacrolimus generally used after intestinal transplant predisposes to the development of food allergy because this report did not find that the increased intestinal permeability was a dose-related phenomenon (12).

Other factors that may increase intestinal permeability after intestinal transplantation are viral infection and graft rejection, which occur in the transplanted intestine itself, as opposed to other organs in the case of solid organ recipients. Isolauri et al. (13,14) have shown that intestinal permeability increases in patients with acute viral gastroenteritis. Graft rejection appears to impair intestinal mucosal barrier function, which recovers very slowly after treatment (15). Patient 3 did have Rotavirus enteritis before the onset of food allergy. Patients 1 and 2 had no acute enteritis and had received relatively low doses of tacrolimus.

More than one factor probably plays a role in predisposing patients to food allergies after intestinal transplantation. Prospective studies are needed to determine the risk of food allergy after intestinal transplantation and to clarify the importance of the donor's allergic history, the recipient's immunosuppressant regimen, changes in permeability of the transplanted intestine, and other factors. Physicians caring for these patients should be alert to the possible de novo appearance of food al-

lergy after intestinal transplantation because of its potential severity.

Editors' note: For a recent commentary on post-transplantation food allergy, see Atkins FM. Systemic FK506 and post transplant food allergy in children. *J Pediatr Gastroenterol Nutr* 2003;37:525-6.

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