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CASE REPORT

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Development of New White Fish Allergy after Bone Marrow Transplantation from a Non-atopic Donor

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Background: Transplant-acquired food allergy has become increasingly recognized in solid organ and bone marrow transplantation. As food allergy has no cure and causes considerable impact on the lives of patients who require strict avoidance of foods to avoid potentially severe or fatal reactions, it is crucial for physicians to better understand the risk factors and mechanisms driving development of food allergy post-transplant. We report a case of new food allergy to whitefish in an elderly patient post-bone marrow transplant in which neither donor nor recipient had a history of atopy. **Methods**: A 70-year-old man experienced an anaphylactic reaction to Swai whitefish (*Pangasius hypophthalmus*) 6 months post-transplant that he had previously tolerated on multiple occasions both pre-transplant and in the preceding months post-transplant. This allergy was investigated by commercial serum specific IgE testing and fresh prick-to-prick skin test to Swai whitefish. **Results**: Fresh prick-to-prick demonstrated large positive reaction to the Swai whitefish with wheal of 10 mm and flare of 22 mm compared to positive histamine control with a wheal/flare of 5x8mm. Serum specific IgE testing to commercial whitefish was negative (specific IgE <0.10kU/L). The patient continues to strictly avoid Swai whitefish but tolerates all other fish and shellfish. **Conclusions**: The unique development of specific Swai whitefish allergy in an elderly man after bone marrow transplant where both donor and recipient had no prior history of atopy strongly supports transplant-related immunomodulation as a major mechanism for transplant-acquired allergy and suggests that that absence of atopy or advanced age may not necessarily be protective.

INTRODUCTION

One of the earliest reports of transplant-related food allergy occurred in a 9-year-old boy who received a matched-related bone marrow transplant from his 7-year-old brother for acute lymphoblastic leukemia [1]. While the recipient patient had no allergic history, his donor brother had significant history of atopy including eczema, allergic rhinitis, and food allergies to egg, peanut, fish, and beans. Six months post-transplant, the patient developed similar food allergies as his brother to egg, nuts, fish, beans, and banana with angioedema and corresponding elevations in IgE to egg and peanut that were not present when checked prior to transplant. Given the similarity of the patient's food allergen profile and his family history of atopy in both donor brother and moth-

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Abbreviations: HSCT, Hematopoietic stem cell transplant.

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er (with allergic rhinitis), initial theories proposed that food allergy could be induced by transplant via transfer of allergen-specific lymphocytes or simply reflect later development of allergy in an already genetically predisposed individual. Numerous other early case reports also described development of new atopy or food allergy after bone marrow transplant from an atopic sibling [2,3], supporting family history of atopy or direct transference as integral risk factors. Similarly, multiple cases of new nut allergy were reported after liver transplant in which the donors had passed from nut allergy-related anaphylaxis. These also suggested direct transfer of allergen-specific lymphocytes, albeit via the resident cells in the liver sinusoids, as a mechanism of transplant-acquired allergy [4,5].

Subsequently, however, new cases surfaced of patients developing food allergy after receiving bone marrow transplants from unrelated donors or developing allergic profiles dissimilar to donor allergic profiles [6]. These reports demonstrated that genetic predisposition in the transplant recipient was not necessary for allergy development, and that alternate mechanisms that did not involve direct transfer of allergen-specific lymphocytes must be at play. Furthermore, in the liver transplant literature, an increasing number of cases appeared where recipients developed new food allergy even when both donor and recipient had no atopic history [7]. In one series of 28 reported cases of liver transplant-associated food allergy by Boyle *et al*., only three donors had history of food allergy [8]. This prompted investigation into the role of immunomodulation and specifically immunosuppressive medications in the development of transplant-associated allergy. Tacrolimus, for example, is known to inhibit IL-2 production, mechanistically skewing T-cells from a Type 1/Th1 to Type 2/Th2 profile, leading some authors to suggest transplant-acquired allergy as a potential adverse effect of tacrolimus therapy. In one case report, tacrolimus use was correlated with significant elevation of IgE levels as high as 80,000 IU/mL compared to 190 IU/mL pre-treatment, and subsequent reduction in tacrolimus trough level resulted in decreased serum IgE levels [9]. Tacrolimus is also known to have the unique effect of increasing intestinal permeability, leading to hypotheses that increased intestinal permeability to food allergens may play a role in the development of food allergy [10]. It should be noted, however, that a literature search revealed case reports of food allergy development only with tacrolimus use in transplant [11,12]. No cases of tacrolimus associated food allergy have been reported outside of transplant.

At this time, while the association between transplant and food allergy has become somewhat more clear, the mechanisms and risk factors driving *de novo* food allergy post-transplant remain poorly understood. More case studies are necessary to drive further analysis of these factors. Here we report the first case to our knowledge of development of a specific Swai whitefish allergy post-bone marrow transplant in which both donor and recipient had no atopic history.

CASE PRESENTATION

We report a case of a 70-year-old male with intermediate risk myelodysplastic syndrome who underwent matched unrelated bone marrow transplant after myeloablative conditioning therapy with fludarabine, busulfan, and anti-thymocyte globulin. The unrelated donor had no reported allergic history per the National Marrow Donor Program registry, and it was confirmed that all donors in this registry are screened for allergies. Our recipient patient likewise had no history of food allergy, drug allergy, asthma, atopic dermatitis, or allergic rhinitis. His post-transplant course was relatively uncomplicated with 100% myeloid engraftment. He was placed on daily tacrolimus for rejection prophylaxis. He did have grade 1 colonic graft-versus-host disease found on colonoscopy two months post-transplant, for which he was treated with oral budesonide, and subsequently remained on daily tacrolimus.

Prior to transplant, the patient had been able to eat a specific cornmeal-breaded Swai whitefish of the species *Pangasius hypophthalmus* purchased each time at the same market on a regular basis. It was confirmed with the market that no changes in sourcing, species, or preparation of this product had been made for the last several years. After the patient's stem cell transplant, he continued to consume the exact same whitefish and had tolerated it on five separate occasions without issue. Six months post-transplant, however, the patient developed an anaphylactic reaction to the whitefish. Within 5 minutes of eating four bites of the whitefish, he developed symptoms of immediate vomiting followed by diffuse hives and respiratory distress. No other food was consumed at the time. Despite taking 50 mg of diphenhydramine, he had persistent vomiting and was additionally found by emergency medical services to be hypotensive with a blood pressure of 90/40 mmHg. He was treated with intramuscular epinephrine, additional diphenhydramine, intravenous methylprednisolone, famotidine, and 1 liter of normal saline fluid in a nearby emergency department with immediate resolution of the hives and remainder of his symptoms.

He presented to the Allergy office 2 months after his reaction. The evaluation included serum commercial specific IgE to whitefish (specific IgE <0.10kU/L) as well as other possible seafood contaminants including shrimp, crab, lobster, clam, scallop. All specific IgE testing returned negative at <0.10 KU/L. He then under-

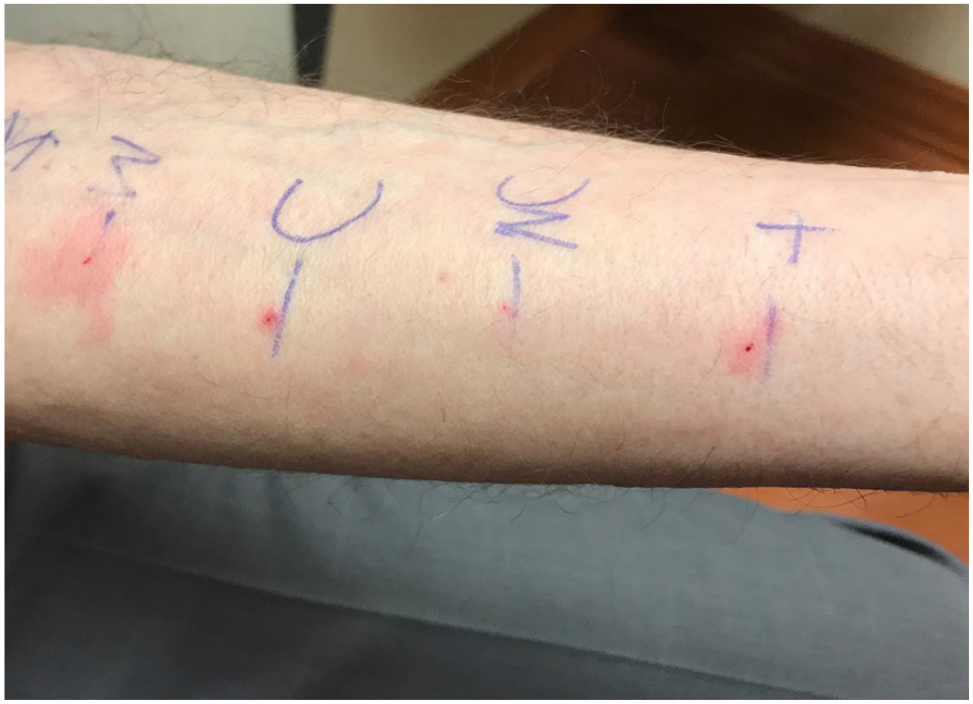

Figure 1. Skin prick testing (left to right), fresh Swai whitefish (W), cornmeal breading (C), negative control (NC), Histamine control (+).

went fresh prick-to-prick skin testing to the exact Swai whitefish prepared from the same market and separately to the cornmeal breading from the fish, and was found to have large positive reaction to only the whitefish component with wheal of 10 mm and flare of 22 mm (Figure 1). Positive histamine control showed wheal/flare of 5/8 mm with appropriate negative control. He was advised to strictly avoid this particular whitefish and has not had any further food reactions since that time. He continues to consume cod, pollock, other finned fish, and shellfish without issue.

DISCUSSION

The development of new food allergy post-transplant has been increasingly described in the transplant literature, predominantly in younger transplant recipients and most commonly reported in liver transplantation. Case reports of new food allergy post-transplant have demonstrated considerable heterogeneity with regards to type of transplant, onset of allergy post-transplant, donor and recipient allergic history, and post-transplant immunosuppressive regimen leading to various proposed mechanisms of allergy development. We report the first case to our knowledge of development of a specific Swai whitefish allergy after bone marrow transplant in which both donor and recipient had no atopic history.

The distinguishing features of this case include the patient's elderly age, the specificity of his allergy to a particular Swai whitefish, his regular tolerance of the food up until 6 months post-transplant, and the notable absence of atopy in both donor and recipient. While transplant-acquired food allergy has been noted in adult populations, it has been much more commonly reported in the pediatric population with the theory that the immature gastrointestinal tract and immune system of children can enhance systemic exposure to dietary antigens and predispose to sensitization. Prevalence of food allergy in general is known to be higher in children compared to adults (8% vs 5%) [13], and the natural history for many common food allergens is to outgrow the food allergy rather than develop new allergy later in life. At least two large studies in liver transplant patients reported that younger age was a significant risk factor in the development of food allergy [14,15]. In one case of a split liver graft in which the donor's left lobe was given to a 19-month-old child and the right lobe was given to a 35-year-old adult patient, only the 19-month-old child developed peanut and egg allergy; the adult recipient remained allergy-free [8]. With regards to transplant-acquired food allergies in the adult population, reported subjects have ranged from age 28-60 years [16]. Our patient received his bone marrow transplant at age 69 years with new onset of food allergy at age 70 years to a food he previously tolerated regularly, strongly supporting the causal effect of transplant and possible immunosuppressive medications on allergy

development and demonstrating that age is not necessarily protective.

The specificity of this patient's food allergy to a particular Swai whitefish is also notable. Fish allergic patients generally have a high incidence of cross reactivity (~50%) to other fish species due to the major cross-reactive fish allergen parvalbumin, leading some practitioners to even advise avoiding other similar fish if diagnosed with fish allergy [17-19]. This patient did not have clinical or laboratory evidence of allergy to other fish at the time of evaluation, and he also had negative serum specific IgE to a commercial preparation of whitefish (Viracor Eurofins, Lee's Summit, MO). The specific antigens covered in this test are not known, however, and this specific lab test has not been approved for diagnostic use by the US FDA [20]. Therefore in this case, fresh prick-to-prick testing to the specific food in question would be considered the diagnostic gold standard. His fresh prick-to-prick testing to the exact Swai whitefish that resulted in the anaphylactic episode and that he had previously been consuming was clearly positive. Given that his donor had no history of fish allergy, this is less likely to be explained mechanistically by the transfer of donor allergen-specific lymphocytes. Rather, the patient likely developed new sensitization to the Swai fish allergen he was repetitively exposed to. The fact that he was able to tolerate the same fish five times in the initial 6 months after transplant (without a preceding long period of avoidance) also suggests that sensitization can occur rapidly. This is supported by at least 12 other cases in which onset of new food allergy occurred within 2 months of transplant, eight of which occurred in adult patients [16].

Finally, acknowledging the limitation of specific allergy screening by the National Marrow Donor Program transplant registry, the apparent absence of atopic history in both donor and recipient in this case suggests causality of bone marrow transplantation itself or post-transplant treatment in the *de novo* development of food allergy. Numerous case reports in bone marrow transplant have reported the apparent direct transfer of specific food allergy and atopy from atopic donors. These were followed by case reports in solid organ transplant of transplant-acquired food allergy despite use of non-atopic donors [7,8], leading to newer theories of immunosuppressant therapy induced allergy. In bone marrow transplant, however, there have been no reported cases to our knowledge of *de novo* food allergy appearing after transplant from a non-atopic donor as in this case. In one case report by Shalit *et al*., a 46-year-old patient developed new dust mite allergy and bronchial asthma, but not food allergy, after bone marrow transplantation from a nonatopic donor [21]. At first glance, direct transfer of specific allergy or predisposition to atopy appears easier to explain. Mature B and T cells with allergen-specific memory and hematopoietic progenitor cells are transferred from donor to recipient in the process of bone marrow transplant and can conceivably go on to produce allergen-specific IgE and cause allergic symptoms. In another case of a 46-year-old male who developed kiwi allergy after receiving myeloablative hematopoietic stem cell transplant (HSCT) from a kiwi-allergic donor, fluorescent in-situ hybridization analysis proved that hematopoietic cells of the recipient completely originated from the donor [22]. *De novo* allergy development in cases of HSCT from non-atopic donors are harder to explain, and more likely result from immunomodulation post-transplant as has been proposed in solid organ transplant. This patient was taking tacrolimus, which can polarize the immune system towards a Type 2/Th2 cell profile by inhibiting IL-2 and other signals that promote the Type 1/Th1 response. A cellular balance towards Type 2/Th2 further enhances the production of IgE and Type 2/Th2 cytokines including IL-5 and IL-13, and promotes the activation of mast cells and eosinophils that result in allergic manifestations.

CONCLUSIONS

Transfer of atopy by bone marrow transplantation is an increasingly well-recognized possibility. However, this case highlights the fact that "transfer" may not be the appropriate term, especially with increasingly reported cases of *de novo* food allergy and atopy post-transplant where neither donor nor recipient have an atopic background. Instead, there are likely rapid immune changes occurring post-transplant to dietary antigen exposures that are enabled by a disrupted cellular milieu and that are less related or unrelated to genetic predisposition and age. As the reported number of cases of *de novo* allergy post-transplant increases, there should be consideration towards development of a centralized reporting registry for transplant acquired allergy. Only through critical analysis of larger cohorts of patients can we hope to better understand the underlying risk factors and pathobiologic mechanisms behind transplant-acquired allergy.

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