
Transfer of atopy following bone marrow transplantation

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Background: Bone marrow transplantation is an optimal treatment of acute leukemia and aplastic anemia. Allergic manifestations in recipients long after bone marrow transplantation have been reported. A case involving transfer of atopy manifested as food allergy-induced-atopic dermatitis is reported.

Methods: The donor and the patient were investigated by prick tests and RAST to the same food allergens. Single blind, oral challenge to egg documented food allergy in the recipient.

Results: A 5-year-old boy without history of atopy developed severe atopic dermatitis after bone marrow transplantation from his HLA-identical sister for acute lymphoblastic leukemia. The patient's course had been marked previously by acute graft versus host disease and cytomegalovirus infection. Immunoallergic evaluation showed an exquisite sensitization to egg, peanut, and soybean. Total IgE was 6400 KIU/L. Concomitantly, the donor showed the same sensitizations. Absolute avoidance resulted in the regression of atopic dermatitis. Subsequently, new sensitization to wheat flour, *Dermatophagoides pteronyssinus*, birch, and plantain pollens was detected. The donor developed asthma.

Conclusions: This case gives evidence of the transfer of sensitization from donor to recipient. The passive transfer of memory cells within the bone marrow inoculum is a possible mechanism. The current concept of allergy supports down regulation of Th1 cells to the benefit of Th2 cells. Additional deregulation induced by acute graft versus host disease, cytomegalovirus infection, and immunosuppression is possible.

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INTRODUCTION

Syngeneic or allogeneic bone marrow transplantation is the ideal treatment of some forms of acute leukemia and aplastic anemia. In the absence of chimerism, the donor's lymphoid stem cells reconstitute the recipient's immune system.¹ Observations of allergic manifestations in recipients long after bone marrow transplantation suggest that there may be a transfer of donor-derived sensitized mature lymphoid cells.²⁻⁷ We report here a case involving transfer of atopy initially mani-

fested as atopic dermatitis related to food allergy that developed after bone marrow transplantation.

CASE REPORT

Child B, a 5 1/2-year-old boy, underwent allogeneic bone marrow transplantation during a second complete remission from acute lymphoblastic leukemia following early-onset meningeal complication. The donor, 2 1/2 years of age, was B's sister. Donor and B were HLA-A, -B, and DR-identical. The mixed lymphocyte culture reaction was negative. Donor had blood group A+. Serologic tests in the donor for cytomegalovirus, HIV-1 and 2, hepatitis B and C, Epstein Barr virus, and toxoplasma were negative, while serologic tests for herpes simplex virus and herpes zoster were positive for IgG. During a hospital stay for a pre-bone marrow transplantation workup,

the donor developed infectious mononucleosis (mononucleosis syndrome with fever and a positive infectious mononucleosis test). The recipient's blood group is O+. Serologic tests for HIV-1 and 2 and toxoplasma were negative. Serologic tests for cytomegalovirus was positive for IgG. Myelogram and cerebrospinal fluid were normal.

B underwent total body irradiation nine days before bone marrow transplantation. This was followed by chemotherapy consisting of cytarabine and alkeran for one day. Prophylaxis of graft versus host disease included a combination of cyclosporine A and methotrexate. B also was treated with acyclovir and gammaglobulin since serologic tests showed that he was cytomegalovirus positive.

The clinical course after bone marrow transplantation was marked by a febrile episode on day 7 which regressed with amphotericin B and then fluconazole. Seven weeks later, this child was again hospitalized 1 week after discharge for diarrhea with a vesicular cutaneous eruption on the inner aspect of the thighs suggesting acute graft versus host disease. Improvement followed corticosteroid therapy.

A myelogram showed complete remission with a very good engraftment since all cells were XX corresponding to those of the donor.

In December, 1992, 2 1/2 months after bone marrow transplantation, B presented with cytomegalovirus viremia, without fever or internal organ involvement. Treatment with ganciclovir resulted in viremia regression. In April, 1993, severe eczema developed with sites typical of atopic dermatitis (antecubital and popliteal fossae, wrists) with secondary lesions from scratching because of intense pruritus.

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Table 1. Results of the Evaluation

Donor			Allergens	Recipient			May, 95
August, 93	August, 94	May, 95		August, 93	Nov, 93	August, 94	
P	P (RAST)	P		P (RAST)	P	P (RAST)	P
3 mm	3 mm	3 mm	9% codeine	3 mm	3 mm	2.5 mm	4 mm
0	3 (1.14)	1.5	<i>D. pteronyssinus</i>	0	0	2.5 (17.9)	2
0	0	0	Cat epithelia	0	0	2.5	1.5
0	0	0	Gramineae	0	0	0	3
0	0 (0.35)	0	Silver birch	1	0	2.5 (32.4)	1
0	0	0	English plantain	0	0	3	1
0	0	0	Latex	0	0	2 (13)	1
0	0 (0.47)	0	Peanut	5 (38)	8	12 (18)	4
2.5	6 (1.23)	2	Egg white	6 (65)	4	11.5 (17.7)	3
0	2 (0.95)	1	Wheat flour	0 (13)	0	0 (12.6)	0
0	0	0	Egg yolk	1.8	8	7 (10.4)	2
0	0 (0.65)	0	Milk	0 (0.3)	0	0 (8)	1
1	0 (0.72)	0	Green soybean	5 (9)	1	3.5 (8.71)	2
285		497	Total IgE (IU/L)	6400	3466	2080	1865
Constant			Peanut lip challenge test			+	
food							
tolerance							
			Egg oral challenge test	+ (1 g)		– (1 g)	

P = prick--test wheal size (mm).

Rast = (IU/L).

This child was hospitalized in August, 1993 for an allergy evaluation (11 months after bone marrow transplantation) while atopic dermatitis had been established for 5 months. All immunosuppressor drugs had been discontinued since June, 1993. The patient's family history revealed that his father had allergic rhinitis to mites. The donor had had atopic dermatitis at 3 weeks of age, colic, and crying episodes when bottle-fed, suggesting an allergy to cow milk proteins. Atopic dermatitis gradually abated by age 1 year. At 3 years of age, she had only dry skin on the anterior chest and periumbilical areas. B had no history of any allergic disorder before bone marrow transplantation.

The allergy evaluations (Table 1) in the donor and B involved prick skin tests to routine airborne allergens and food allergens: *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Alternaria*, *Aspergillus*, pollens of English plantain, pellitory, silver birch, mugwort, couch grass, timothy grass, thuya, ash, cat and dog epithelia and latex; milk, egg white, egg yolk, peanut, green soybean, white soybean,

wheat, almond, walnuts, cashew, Brazil nuts, hazel nuts, and pistachio nut. A prick test was considered positive when a control with physiologic saline was negative and the diameter of a wheal produced by the test was greater than 2/3 of a codeine control. Total IgE and specific IgE were assayed using the Pharmacia and the Cap RAST test. Depending on results of these investigations, a single blind, oral challenge tests (whole raw egg: 1 g; white soybean: 3 g then 7 g; peanut oil: 5 mL followed by 10 mL and a lip challenge test to peanut were carried out in B.

Skin tests on B in August 1993 showed no sensitization to airborne allergens, but exquisite sensitization to egg, peanut, and soybean. Oral challenge test to egg documented a true allergy (reactive dose: 1 g). Total IgE levels were very elevated at 6400 KIU/L. An intradermal reaction to tuberculin, positive before bone marrow transplantation, was negative. Concomitantly, B's sister showed sensitization to egg and a prick skin test that was doubtful for green soybean. She showed normal tolerance to ingestion of egg. Total IgE was elevated for the

child's age at 255 IU/L. An intradermal reaction to tuberculin was negative.

Absolute avoidance of egg, soybean, and peanut proteins was initiated and resulted in improvement and regression of atopic dermatitis. A repeat evaluation, in August, 1994, showed the absence of any atopic dermatitis lesion, simultaneous development in donor and B of sensitization to *Dermatophagoides pteronyssinus* and to wheat, and a simultaneous increase in sensitization to egg white. At the same time the donor developed asthma. Sensitization to other allergens was also noted in B, namely silver birch pollen and latex. Positive lip challenge test documented food allergy to peanut. With the elimination diet, the patient's clinical condition was excellent, and IgE decreased from 6400 IU (August, 1993) to 3466 IU (November, 1993) and from 2080 IU (August, 1994) to 1865 IU (May, 1995).

DISCUSSION

Bone marrow transplantation is a valuable therapeutic option in some hematologic disorders such as the leukemias or aplastic anemias.¹ B is an example

of the best possible case (except for identical twins), since HLA groups were identical and the mixed lymphocyte culture reaction was negative. Allogeneic bone marrow transplantation was performed in this patient and it can be concluded that there was a chimerism since on two occasions all cells in the karyotype were XX in this boy.

B however developed moderate acute graft versus host disease. Among clinical manifestations, possible eczematiform cutaneous involvement is recognized.⁸ Vesicular lesions of dermatitis promptly regressed with cyclosporine and corticosteroid therapy. Skin lesions of eczema recurred a few months later and were not related to acute graft versus host disease. Sites were typical of atopic dermatitis suggesting atopy precipitated by immunosuppressor therapy, graft versus host disease or cytomegalovirus infection. Since the cellular support of atopy is a subpopulation of T helper cells (functional profile of Th₂ cells),^{9,10} skin manifestations could only have been caused by lymphocytes from the donor, B's sister.

Transfer of atopy by bone marrow transplantation is a well-recognized possible complication.²⁻⁷ Animal studies have previously shown that antibodies including IgE can be transferred after infusion of cells from bone marrow, spleen, or thymus from a donor.¹¹⁻¹³ In humans, the transfer of IgG cells after bone marrow transplantation is well-known. Antigen-specific IgG cells have been shown to be the same in the recipient's bone marrow as those in the donor.^{14,15}

Agosti et al⁷ studied the outcome in recipients of bone marrow transplantation from allergic donors. Hypersensitivity was detected in recipients by prick skin testing with 17 airborne allergens and measurement of specific IgE against *Dermatophagoides farinae*. Twelve donor/recipient pairs were enrolled in the study. An allergy evaluation was performed before bone marrow transplantation at day 30, day 100 and more than 1 year after bone marrow transplantation for recipients. Among 11 recipients who survived

more than a year after bone marrow transplantation, 8 had persistent production of IgE including 50% with positive skin tests. The author formulated a hypothesis that the presence of specific IgE responses more than a year after bone marrow transplantation can only be related to acquisition of B lymphocytes from the donor. It cannot involve passive transfer of IgE because the half-life of serum IgE is very short, ranging from 1.8 days in normal subjects to 4.3 days in atopic patients.¹⁶ Even if passively transferred serum IgE binds to mast cells of the recipient, the half-life does not exceed 3 weeks, so that it has been shown that the skin reactivity of a nonallergic recipient after infusion of serum from an allergic donor does not persist beyond 3 months.¹⁸ Consequently, sporadic passage of blood products containing immunoglobulins that might occur during the graft does not appear to be a major mode of transfer of allergen-specific IgE.¹⁷

There are many factors to explain IgE-producing B-cell clones transferred from donor to recipient. Detection of skin test positivity in the donor+/recipient- group in the immediate post-bone marrow transplantation period suggests that IgE-producing B-cell clones may be activated by allostimulatory factors in the recipient environment.⁷ The persistence or emergence of allergen-specific reactivity 1 year after grafting shows that B-cell clones with IgE specific memory were transferred and entered the bone marrow and peripheral lymphoid organs of the recipient. This IgE synthesis was first attributed to insufficient suppression of CD4 by CD8.¹⁹ Conversely, it was noted that IgE is not increased in recipients who develop chronic graft versus host disease, a disease during which CD8 is increased.^{7,8} No recent report has been published assessing the status of Th₁ and Th₂ cells.

In this case there was indeed transfer of allergic response from donor to recipient. The immune system reconstituted in the recipient came from the donor because a study of bone marrow

chimerism showed that all cells were XX of the donor's type. As soon as the first evaluation was performed, hypersensitivity was more enhanced in the recipient than in the donor (IgE: 285 IU/L in donor, 6400 in B). Two years after bone marrow transplantation, the recipient showed sensitization to other allergens (airborne allergens and wheat flour). It is interesting to note that, concomitantly, the donor also exhibited sensitization to *Dermatophagoides pteronyssinus* and wheat. This concomitant progression confirms the "genetic programming of hypersensitivity" expressed in the same environment.²⁰

Since the identification of 2 types of CD4+ lymphocyte subpopulations, the mechanisms that intervene in the production of IgE by B-cell clones are now better understood. Th₁ and Th₂ subpopulations have been identified through their different patterns of cytokine secretion. Th₁ cells synthesize IL-2, INF- γ and TNF- β , and Th₂ cells IL-4, IL-5 and IL-10.^{9,10} It now is clear that activation of Th₂ cells initiates IgE-synthesis.²¹

A hypothesis can be formulated whereby the imbalance between Th₁ and Th₂ cells is much more accentuated in the recipient than in the donor. This means that factors responsible for this have to be discussed. There can be many such factors. The child reported here presented with cytomegalovirus infection 4 months before atopic dermatitis. Cytomegalovirus precipitates B-cell proliferation with synthesis of nonspecific IgE.²² He also developed acute graft versus host disease during which there was a transient increase in IgE²¹ and a decrease in CD8.²³ This may have enhanced the function of Th₂ cells. In addition, diarrhea may have caused intestinal inflammation resulting in increased permeability and enabling increased passage of food allergens and precipitating the development of sensitization to certain foods.

Last, the role of immunosuppressor therapy has to be considered. Chen demonstrated that cyclosporine A can increase IgE-dependent antibody response in mice after exposure to an

antigen.²⁴ Cyclosporine A may be able to trigger an imbalance between Th₁ and Th₂ cells to the benefit of Th₂ thus inducing IgE synthesis. Similarly, it has been shown that cyclosporine A increases the expression of Fc RIIε in B-cells of hybridomas²⁵ thus enhancing IgE responses.

With progressive movement away from the action of these three factors, a gradual decrease in Th₂ activity can be hoped for. A decrease in total IgE from 6400 to 2080 IU/L and even to 1865 IU/L was observed in the recipient reported here, with a gradual move away from the three above-mentioned factors. A favorable outcome for hypersensitivity cannot be confirmed because of the manifest development of specific IgE.

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