

Allergy development after bone marrow transplantation from a non-atopic donor

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Summary

Background Transfer of allergy from atopic bone marrow donors to recipients is known to occur. Development of allergy in a non-atopic patient transplanted from a non-atopic donor is an unfamiliar phenomenon in clinical practice.

Objectives To clarify the course of events causing a bone marrow recipient to acquire an allergic disease in such non-conducive circumstances.

Methods Full medical history, prick and intradermal skin tests, and serum IgE levels were obtained from both donor and recipient patients. DNA and red blood cell phenotype analyses were used to detect the degree of chimerism.

Results Only the recipient patient showed positive specific IgE antibodies and skin tests to house dust mite. The recipient patient displayed 100% donor chimera, based on all engraftment markers sought.

Conclusion Full engraftment after allogeneic bone marrow transplantation may be associated with modulation of T and B cell function, which in turn could cause the onset of allergic disease after bone marrow transplantation.

Keywords atopy, bone marrow transplantation, graft-vs-host disease

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Introduction

Allogeneic bone marrow transplantation (BMT) in humans is an established treatment for severe aplastic anaemia, various malignancies, genetic disorders and for several immune deficiency diseases [1]. Several authors have demonstrated early transient increased serum levels of polyclonal IgE antibodies in recipients of bone marrow grafts [2]. These elevated IgE titres are usually associated with acute graft-versus-host disease (GVHD) or viral infection [2, 3]. However, no clinical manifestations of allergy have been noted during such elevations in IgE levels. Transfer of allergy from an atopic donor to BMT recipients has been described in a number of case reports [4, 5]. Agosti et al. [6] showed the transfer of allergen-specific IgE-mediated hypersensitivity from allergic donors to recipients surviving more than 1 year post BMT. All the recipients either acquired or experienced exacerbation of allergic disorders, including rhinitis, asthma and urticaria. Laboratory evidence of hypersensitivity to allergens was noted.

In contradistinction we present the development of allergy in a non-atopic patient transplanted from a non-atopic donor. In order to illustrate the acquisition of house dust mite hypersensitivity, a description of the patients and treatment received is provided. Immunomodulation during the post-transplant

period is a possible contributory factor in the allergic pathogenesis.

Case report

A 23-year-old male was admitted with aplastic anaemia of unknown aetiology, rapidly progressing to the severe form, according to international criteria [7]. Until his present illness, the patient had been in good health, with no history of allergic signs and symptoms, such as rhinitis, asthma, eczema or urticaria. The patient underwent allogeneic BMT from his HLA-matched, mixed lymphocyte culture non-reactive brother. The sibling had a negative history for the above-mentioned allergic diseases. Pre-transplant conditioning of the patient included total lymphoid irradiation (TLI; 25 cGy/day $\times$ 5 days) followed by intravenous (i.v.) cyclophosphamide 50 mg/kg/day $\times$ 4 days. GVHD prophylaxis included methotrexate i.v. 10 mg/m² on days +1, +3, +6 and +11 (after transplantation). The post-transplant course was complicated by acute mild GVHD (grade I) manifested only as a skin rash that was successfully treated with prednisone, 1.5 mg/kg/day, with total resolution within 2 weeks. The steroid treatment was tapered and withdrawn on day +50. The patient displayed rapid haematopoietic engraftment with normal blood counts on day +28.

A year after the BMT, the patient began to suffer from bronchial asthma accompanied by watery rhinitis, both of which were treated successfully with bronchodilators, antihistamines, plus inhaled and intranasal steroids. The clinical course

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of the *de novo* bronchial asthma and rhinitis were characterized by the typical fluctuating nature, requiring short courses of oral steroids. Pulmonary function tests – performed during the asthma attacks – showed moderate airflow obstruction, which improved after inhalation of a β -agonist. Both prick and intradermal skin tests with a battery of 32 common allergens were strongly positive only to house dust mite (*Dermatophagoides pteronyssinus* and *D. farinae*) – weal/flare 6/10 mm for prick test. IgE antibodies specific to mites (D₁ and D₂ Pharmacia Diagnostics, Uppsala, Sweden), were +4 [radioallergosorbent test (RAST) score], whereas IgE antibodies to other airborne allergens were negative. The serum obtained prior to BMT was re-examined and found negative for IgE antibody to mite antigens. Total IgE levels were normal pre- and post-BMT (52 IU/mL and 80 IU/mL, respectively).

Both patient and donor lived in the same place (a kibbutz). Upon the appearance of the allergy in the BMT patient, the same battery of skin tests were performed (repeated three times) in the donor, with consistent negative results for all tests. The donor's IgE levels were normal (63 IU/mL) and repeated tests for specific IgE antibodies to aeroallergens, including house dust mite, were negative. It is noted that the patient presented with the classical allergic symptoms on exposure to house mite environments, rendering further testing unnecessary.

To detect chimerism post-BMT, engraftment markers were sought using various techniques including DNA analysis using the polymerase chain reaction–variable number tandem repeats (PCR–VNTR) and revealed donor origin haematopoiesis. Mapping of the patient's original VNTR was reconstructed from fibroblasts obtained by skin biopsy. The reconstruction was necessary as the PCR–VNTR technique was not available at the time of the patient's marrow transplantation. The degree of chimerism demonstrates the presence 100% donor cells (Fig. 1). To date, the patient is in good health and is continually followed-up for manifestations of bronchial asthma and rhinitis.

Discussion

The chemoradiotherapy delivered to patients undergoing BMT and the allogeneic immunocompetent cells may promote pathogenic immune reactions in the host.

Recipients developing thrombocytopenia after transplantation of marrow from donors with antiplatelet antibodies

were reported. In these patients thrombocytopenia resolved; however, persistent autoantibody production continued [8]. A further instance of donor-acquired disease is illustrated by the transfer of antiacetylcholine receptor antibody-producing cells from a donor with myasthenia gravis resulting in myasthenia gravis in the recipient [9]. Adoptive transfer of allergen-specific IgE B cell clones from marrow donors to recipients may result in transfer of atopic symptoms. After transplanting non-allergic recipients with marrow from skin test-positive donors with clinically determined allergies, the majority of long-term survivors acquired positive skin test reactivity, clinical allergic rhinitis and some recipients became asthmatic [10–24]. This course of events demonstrates the transfer of IgE-mediated hypersensitivity to BMT recipients. Conversely, allogeneic BMT can eliminate allergic manifestations in positive recipients when transplanted from non-atopic donors, thereby correcting allergic and autoimmune diseases [15, 16].

In contrast to the transfer of allergy or autoimmunity by means of BMT, as described above, the patient presented is unique in the acquisition of allergic signs and symptoms post-BMT, which can not be attributed to the immune system of the sibling donor. The lack of an atopic family history strengthens the role of the marrow transplantation as the causative factor in the development of the patient's dust mite allergy. It should also be noted that both donor and recipient have always lived in close proximity, worked similarly outdoors in agriculture and shared the same sleeping and living arrangements, which dismisses the involvement of environmental factors in the development of the allergy in the recipient. During long-term follow-up of the donor, no manifestations of allergic disease were detected. Therefore, the course of allergic events is probably related to post-transplant immunomodulation, especially as the patient displayed full donor engraftment, i.e. acquired the haematolymphopoietic system, including antigen-presenting cells of donor origin. Haematopoietic engraftment and the ontogenetic development of the immune system can be dysregulated, by graft-vs-host reaction and its prevention, or therapy, with immunosuppressive/immunomodulatory treatment [16, 17].

Allogeneic BMT is a mode of therapy that may polarize immune deviation toward the T helper 2 (Th2) cell pattern, and thus be conducive to establishment of allograft tolerance and long-term engraftment. Evidently, Th1-type immune activation is often manifested during allograft rejection, as shown by the presence of elevated levels of IL-2, IFN γ and cytotoxic T cells [18, 19]. In addition, Th2 cytokines (IL-4 and IL-10) have

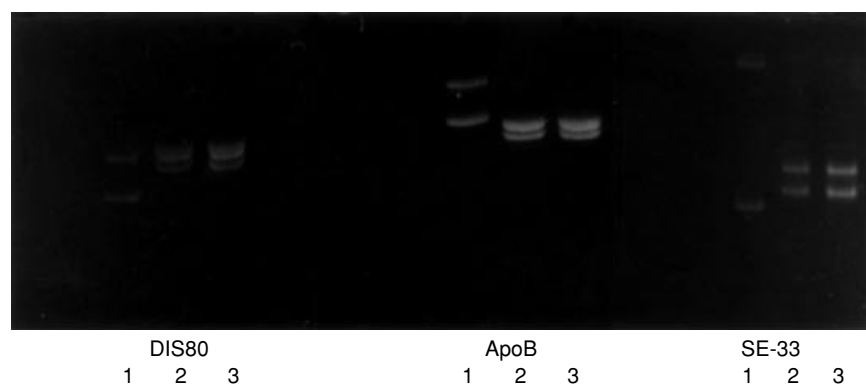


Fig. 1. Engraftment was monitored by DNA amplification of samples from patient prior to bone marrow transplantation (BMT; lane 1) post-BMT (lane 2) and from HLA-compatible donor (lane 3). Reactions were carried out in 25- μ L aliquots using 0.5 units of Taq polymerase (MBI) in a MJR thermocycler (Watertown, MA, USA). Three VNTRs (variable number of tandem repeats) were used for this purpose: ApoB, DIS80 and SE-33. The amplification products were separated on 2% agarose gels; the gels were visualized with ethidium bromide under ultraviolet light.

been shown to be up-regulated in allograft recipients receiving tolerating therapies and in association with the GVHD [18–20]. A well-established association between Th2-type cytokine production and allergic diseases/manifestations is known, on the one hand, and between Th1-type cytokine production and protection from allergic predisposition, on the other [20].

It is suggested that, in the present patient, allergic susceptibility established itself *de novo* after marrow transplantation. It is reasonable to assume that modulation of B and T cell function and shift of the T cell effector phenotype as a result of the GVHD (or its treatment) accounts for the induction of the allergic disease in this case.

References

- 1 Armitage JO. Bone marrow transplantation. *N Engl J Med* 1994; 330:827–38.
- 2 Walker SA, Riches PG, Wild G et al. Total and allergen-specific IgE in relation to allergic response pattern following bone marrow transplantation. *Clin Exp Immunol* 1986; 66:633–9.
- 3 Walker SA, Rogers TR, Perry D, Hobbs JR, Riches PG. Increased serum IgE concentration during infection and graft-versus-host disease after bone marrow transplantation. *J Clin Pathol* 1984; 37:460–2.
- 4 Bellou A, Kanny G, Fremont S, Moneret-Vautrin DA. Transfer of atopy following bone marrow transplantation. *Ann Allergy Asthma Immunol* 1997; 78:513–6.
- 5 Olaguibel J, Almodovar A, Giner A et al. Passive transfer of contact sensitivity to colophony as a complication of an allogeneic bone marrow transplant. *Contact Dermatitis* 1989; 20:182–4.
- 6 Agosti JM, Sprenger JD, Lum LG et al. Transfer of allergen-specific IgE-mediated hypersensitivity with allogeneic bone marrow transplantation. *N Engl J Med* 1988; 319:1623–8.
- 7 Camitta BM, Storb R, Thomas ED. Aplastic anemia: pathogenesis, diagnosis, treatment and prognosis. *N Engl J Med* 1982; 306:645–52.
- 8 Minchinton RM, Waters AH, Kendra J, Barrett AJ. Autoimmune thrombo-cytopenia acquired from an allogeneic bone-marrow graft. *Lancet* 1982; 2:627–9.
- 9 Smith CI, Aarli JA, Biberfeld P et al. Myasthenia gravis after bone marrow transplantation. Evidence for a donor origin. *N Engl J Med* 1983; 309:1565–8.
- 10 Saarinen UM. Transfer of latent atopy by bone marrow transplantation? A case report. *J Allergy Clin Immunol* 1984; 74:196–200.
- 11 Tucker J, Barnetson RS, Eden OB. Atopy after bone marrow transplantation. *Br Med J Clin Res Ed* 1985; 290:116–7.
- 12 Geha RS, Rappaport JM, Twarog FJ, Parkman R, Rosen FS. Increased serum immunoglobulin E levels following allogeneic bone marrow transplantation. *J Allergy Clin Immunol* 1980; 66:78–81.
- 13 Saryan JA, Rappaport J, Leung DY, Parkman R, Feha RS. Regulation of human immunoglobulin E synthesis in acute graft-versus-host disease. *J Clin Invest* 1983; 71:556–64.
- 14 Ringden O, Persson U, Johansson SG et al. Markedly elevated serum IgE levels following allogeneic and syngeneic bone marrow transplantation. *Blood* 1983; 61:1190–5.
- 15 Wahn V, Laws HJ, Bode CP, Burdach SE. Cure of latex allergy by bone-marrow transplantation. *Eur J Pediatr* 1999; 158:88.
- 16 Benner R, Wolters EA, Bril H, Molendijk A, van Oudenaren A. Regulation of delayed type hypersensitivity to host histocompatibility antigens during graft-versus-host reactions. *Immunol Rev* 1985; 88:25–57.
- 17 Pritchard LL, Huchet R, Bruley-Rosset M, Riche N, Mishal Z, Halle-Pannenko O. Induction and suppression of delayed-type hypersensitivity to non-MHC antigens during lethal graft-versus-host reaction. *J Immunol* 1992; 149:45–52.
- 18 Nash RA, Storb R. Graft-versus-host effect after allogeneic hematopoietic stem cell transplantation: GVHD and GVL. *Curr Opin Immunol* 1996; 8:674–80.
- 19 Strom TB, Roy-Chaudhury P, Manfro R et al. The Th1/Th2 paradigm and the allograft response. *Curr Opin Immunol* 1996; 8:688–93.
- 20 Durham SR, Till SJ. Immunologic changes associated with allergen immunotherapy. *J Allergy Clin Immunol* 1998; 102:157–64.