

LETTER TO THE EDITOR

Increase in allergy following donor lymphocyte infusions

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Development of atopy following bone marrow transplantation is recognized in the literature, although predominantly restricted to case reports. The principal mechanism suggested for this has been transfer of mature memory B cells with the graft,¹ although one paper postulates that the transplant procedure itself can contribute or be solely responsible.² We report the case of a patient who was not atopic but developed multiple allergies after bone marrow transplantation from an atopic sibling, with worsening allergy symptoms following donor lymphocyte infusions (DLI). The phenomenon of worsening allergy symptoms with DLI has not been reported previously.

A 41-year-old lady underwent reduced-intensity bone marrow transplantation following relapse of non-Hodgkin's lymphoma (follicle centre cell lymphoma stage IIIA). Three years previously, she had been treated with six cycles of CHOP (Cyclophosphamide, Doxorubicin, Vincristine and Prednisolone). After relapse, she was treated with three cycles of CVP (Cyclophosphamide, Vincristine, Etoposide and Prednisolone) and Rituximab, which had resulted in clinical remission. The donor was her human leukocyte antigen (HLA)-identical brother. Before developing lymphoma, she had been well with no history of atopy or allergy.

Pre-transplant conditioning comprised BCNU 300 mg/m² day –6, etoposide 200 mg/m² and cytarabine 200 mg/m² days –5 to –3 and melphalan 140 mg/m² day –2 with Alemtuzumab 20 mg days –6 to –2 followed by a donor stem cell infusion on day 0. She also received cyclosporine to a target blood level of 200 µg/l for prophylaxis of graft-versus-host disease, which was subsequently stopped on day +90. Unfortunately, peripheral blood chimerism studies 7 months post transplant showed a shift towards recipient cells. Consequently, the patient was given two DLI, at 5×10^6 and 1×10^7 T cells/kg, 10½ and 14 months after transplantation. This resulted in 100% donor cells on subsequent chimerism testing.

Three months after transplantation, the patient developed eczema. Two months later, she developed urticaria and diarrhoea following ingestion of bananas. In the spring following her second DLI, she started to develop symptoms of rhinitis, which remained throughout the year but were more pronounced in spring and summer. She also started to develop oral itching on eating avocado.

The donor, her brother, was atopic with multiple allergies since childhood. In childhood, he had been diagnosed as allergic to bananas and suffered from eczema, hayfever and asthma. Skin prick testing in his childhood

had showed positive wheal responses to house dust mite, dog, pollens and moulds.

Skin prick testing of the patient showed positive wheal responses to house dust mite, grass pollen, tree pollen, cat and dog dander and negative responses to moulds and silver birch pollen. Her serum total immunoglobulin (Ig)E was elevated at 173.0 kU/l and specific IgE for banana was 1.45 kUA/l and avocado was 0.83 kUA/l. Serum before her bone marrow transplant was obtained. This showed a normal total IgE of 33.0 kU/l and negative specific IgE (<0.35 kUA/l) for banana and avocado. Her brother's serum before bone marrow transplantation was obtained and tested. This showed negative specific IgE for banana, avocado and cat (<0.35 kUA/l) with positive specific IgE for house dust mite (32.7 kUA/l), dog (1.73 kUA/l) and grass pollen mix.

Only one prospective study so far has evaluated the likelihood of development of allergy post-allogeneic bone marrow transplantation.¹ The authors of the study concluded that allergen-specific IgE could only be transferred by allergen-specific memory B cells. It could not be due to passive transfer of IgE because the half-life of IgE is very short (up to 4.3 days in atopic patients),³ and even with passively transferred IgE binding to mast cells, its half-life does not exceed 3 weeks.⁴

Other factors have also been suggested as responsible for the development of atopy post transplantation. Shalit *et al.*² concluded that the development of allergy must be related to post transplant immunomodulation as full engraftment occurred in their patient and no allergic disease was detected in long-term follow-up of the HLA-matched sibling donor. They suggested that bone marrow transplantation induces a T-helper 2 (Th2) bias in the immune system, favouring allograft tolerance and long-term engraftment. A T-helper 1 (Th1) pattern of immune activation is seen in graft rejection, as evidenced by high levels of interleukin-2, interferon-γ and cytotoxic T cells.^{5–6} Th2 responses are associated with allergy.

To date, development of atopy post-bone marrow transplantation has primarily been attributed to transfer of allergen-specific memory B cells. Against this in our case is the administration of Alemtuzumab, a monoclonal antibody that depletes both T and B cells and persists in the circulation during the post transplant period.⁷ Compared to T-cell-specific antibodies, Alemtuzumab is associated with a lower incidence of Epstein–Barr virus-related post transplant lymphoma,⁸ which is also mediated by transfer of donor B cells. Nonetheless, we believe that transfer of allergen-specific memory B cells is the most likely mechanism in the case of our patient. She had no allergies before transplantation and her allergic symptoms increased with increasing donor chimerism and recurred

following DLI. Immunomodulation and the change in the internal milieu associated with bone marrow transplantation may however play a part as well, although it is uncertain how much this is responsible for the development of atopy. In our patient, immunomodulation might have contributed as well, given her shared genetic makeup with the donor and the negative donor-specific IgE for some allergens to which our patient subsequently tested positive (although long-term donor avoidance of allergens might account for the negative test). As one editorial suggests, it seems surprising that allergy post-bone marrow transplantation is as uncommon as it is,⁹ although frequency of atopy post-bone marrow transplantation needs to be further assessed.

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References

- 1 Agosti JM, Sprenger JD, Lum LG, Witherspoon RP, Fisher LD, Storb R *et al.* Transfer of allergen-specific IgE-mediated hypersensitivity with allogeneic bone marrow transplantation. *N Engl J Med* 1988; **319**: 1623–1628.
- 2 Shalit M, Amar A, Or R. Allergy development after bone marrow transplantation from a non-atopic donor. *Clin Exp Allergy* 2002; **32**: 1699–1701.
- 3 Dreskin SL, Goldsmith PK, Strober W, Zech LA, Gallin JI. Metabolism of immunoglobulin E in patients with markedly elevated serum immunoglobulin E levels. *J Clin Invest* 1987; **79**: 1764–1772.
- 4 Loveless MH. Immunological studies of pollinosis II. Passive sensitisation of man through transfusion. *J Immunol* 1941; **41**: 15–34.
- 5 Nash RA, Storb R. Graft-versus-host effect after allogeneic stem cell transplantation: GVHD and GVL. *Curr Opin Immunol* 1996; **8**: 674–680.
- 6 Strom TB, Roy-Chaudhury P, Manfro R, Zheng XX, Nickerson PW, Wood K *et al.* The Th1/Th2 paradigm and the allograft response. *Curr Opin Immunol* 1996; **8**: 688–693.
- 7 Morris EC, Rebello P, Thomson KJ, Peggs KS, Kyriakou C, Goldstone AH *et al.* Pharmacokinetics of Alemtuzumab used for *in vivo* and *in vitro* T-cell depletion in allogeneic transplantations: relevance for early adoptive immunotherapy and infectious complications. *Blood* 2003; **102**: 404–406.
- 8 Hale G, Jacobs P, Wood L, Fibbe WE, Barge R, Novitzky N *et al.* CD52 antibodies for prevention of graft-versus-host disease and graft rejection following transplantation of allogeneic peripheral blood stem cells. *Bone Marrow Transplant* 2000; **26**: 69–76.
- 9 Gennery AR, Cant AJ. Development of allergy post-bone marrow transplantation. *Clin Exp Allergy* 2002; **32**: 1677–1678.