

EDITORIAL

Development of allergy post-bone marrow transplantation

Bone marrow transplantation is increasingly successful in curing a range of haematological disorders, malignancies and inborn errors of metabolism. Acute graft vs. host disease (GvHD), and infections are the most common complications [1]. The transfer of disease from donor to recipient is well recognized, most notably with infectious agents such as cytomegalovirus [2]. The transfer of an allergy is rare but also well recognized with numerous reports of bone marrow recipients acquiring IgE-mediated hypersensitivity from their donor, to a diverse range of environmental and food allergens [3, 4]. Serum IgE levels often rise in the post-transplant period [5], yet acquired hypersensitivity is unlikely to be due to passively transferred donor allergen-specific IgE. The plasma half-life of unbound transferred IgE is only a few days, and so donor-transferred IgE will have disappeared within 3–4 weeks. Furthermore, IgE levels are often raised in recipients receiving marrow from non-atopic donors [6]. The evidence that serum IgE levels rise with the onset of GvHD or infection is conflicting; some studies report an association, whilst others demonstrate no temporal correlation [7, 8]. The rise is not related to myeloablative chemotherapy as it has been observed in immunodeficient children transplanted without chemotherapy [9]. Serum IgE rise is preceded by an increase in a soluble CD23 product, thought to be a fragment of the low-affinity IgE receptor, and probably released during the immunoregulatory imbalance immediately post-transplantation [10]. In the immediate post-transplant period it is likely that donor-derived IgE-secreting mature B cells are released from the normal T cell regulation, allowing an uncontrolled release of IgE, until regulatory T cells have re-populated [8]. However, GvHD is characterized by cellular degeneration and damage, mediated by activated macrophages and a Th1-type response [11]. At first glance it would seem counter-intuitive to suggest that GvHD is associated with a Th2-related phenomena such as increased IgE production. However, the T cell immunosuppression associated with GvHD, or indeed viral infections such as CMV, may allow IgE-secreting B cells to escape normal T cell suppression and this could well explain an association between GvHD or infection and increased IgE production.

Transfer of atopic disease from an affected donor, to an unaffected recipient is more likely to occur by adoptive transfer of donor allergen-specific B cells, giving rise to immediate hypersensitivity, or by donor allergen-specific T cells (which can survive for many years), leading to delayed hypersensitivity [12, 13]. Such hypersensitivity can be demonstrated by skin prick tests and the presence of allergen-specific IgE some months following transplantation, implying the presence of a population of cells which is long-lived, and able to secrete IgE *de novo*. Most bone marrow transplants are performed for haematological malignancy, and whole, or red cell-depleted marrow is given, with an opportunity for donor-derived 'aberrant' B and T cells to be transferred.

Could transfer of atopic disease occur if only CD34 positive haemopoietic stem cells were transplanted? Clearly, adoptive transfer would not be possible if a pure population of stem cells,

without contamination of mature donor T or B cells, were isolated. However, if an atopic tendency is not simply genetically determined, but also influenced by the microenvironment of the developing immune system, atopy may theoretically develop within a previously non-atopic individual if the reconstituting immune system was driven in a Th2 direction by its surrounding milieu at the time of reconstitution. The report by Shalit et al. in this issue widens the experience of atopy after bone marrow transplantation [14]. They describe symptomatic IgE-mediated house dust mite sensitivity occurring in a patient who received whole marrow from a non-atopic sibling, who lived in the same physical environment. Transfer of allergen-specific lymphocytes is unlikely, as the donor had no evidence of sensitivity on formal skin prick or allergen-specific IgE testing. Their patient had mild grade I skin GvHD in the early transplant period, which is very common, and so it seems unlikely that this alone could have skewed the immune system in a Th2 direction. Thus, other unidentified microenvironmental factors surrounding the lymphoid system may have been responsible. Interestingly, such constitutional environmental factors, rather than a haemopoietic stem cell defect may well be responsible for the hyper-IgE syndrome [15]. In this condition, a 'successful' bone marrow transplantation (BMT) with full donor chimerism in all cell lines did not prevent the re-emergence of very high IgE levels once post-BMT immunosuppression was stopped [16]. This suggests that the transfer of non-atopic cells into a recipient with a microenvironment favouring high IgE production results in high IgE production, although whether the hyper-IgE syndrome truly belongs within the spectrum of atopic disease is very much open to question.

The process of BMT involves many tissues. Whilst it is only allogeneic haemopoietic cells that are transferred, transplant-associated chemotherapy and/or coexisting infection can lead to tissue damage in many sites, particularly in lung and gut, but also capillary vessels and skin [17]. Post-transplant capillary leak syndrome, and idiopathic pneumonitis are well described and associated with massive inflammatory cytokine release [18]. Dendritic cells play a crucial role in initiating and mediating the allergic response, by taking up antigen and migrating to lymphoid tissue to prime naïve T cells. Th1 or Th2 effector function is determined at this point by the cytokine-induced switch of the naïve Th cell. Prostaglandin E₂, an inflammatory product of fibroblasts and epithelial cells, induces early development of a subset of dendritic cells into Th2-promoting cells [19]. Glucocorticoids, widely used to prevent or control GvHD or engraftment syndrome also induce a shift from Th1 to Th2 immunity by modulating expression of IL-12 or IL-12R, allowing dominant expression of Th2 cytokines [20, 21]. It is therefore possible to construct a scenario whereby newly emergent naïve Th cells from the thymus, and B cells from the bone marrow enter an inflammatory milieu generated by post-chemotherapy tissue damage, and aggravated by GvHD or viral-induced tissue damage, and are induced in a Th2 direction. Seen as a whole, these observations show that a donor's atopic tendency may or may not be manifest in a bone marrow recipient and that atopy

may develop in a non-atopic recipient who has received cells from a non-atopic donor. Set alongside the surprising finding that BMT with full donor chimerism did not correct the hyper-IgE syndrome, this strongly suggests that constitutional or acquired microenvironmental factors affecting the developing immune system contribute to the development of atopy in BMT recipients. In the light of this, it is perhaps more surprising that allergy post-bone marrow transplantation seems to be as uncommon as it is.

References

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