LETTER TO THE EDITOR

Acquired allergies in hematopoietic stem cell transplantation recipients: a case series analysis and literature review

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To the editor

Allogeneic hematopoietic stem cell transplantation (alloHSCT) is a potential curative chemoimmunotherapy adopted in various hematologic diseases [1]. A potential human leukocyte antigen (HLA) identical family donor is not always available. For most patients (approximately 70%) who lack a HLA identical sibling, alternative donors include unrelated donors (URD), haploidentical donors and cord blood units (CBU) [2].

Nowadays, the selection of a HSC donor is based on medical history and laboratory considerations similar to those used for other blood components. This process involves a dynamic balance between ensuring HSC availability and ensuring its safety. Currently, a person is ineligible for donation due to medical conditions that may expose the donor to health risks and that could compromise the safety of the apheresis procedure and the resulting product [3,4,5] . The allergy history of the donor may not be mentioned; although this anamnestic detail is not routinely passed on to the transplant center, it may have a significant clinical relevance[6]. An acquired-allergy of the host is a rare event that range from mild to severe reactions. This issue can occasionally mimic graft versus host disease (GvHD) and the clinical manifestation of allergy may be different in the donor pre-transplant versus the recipient post-transplant.

We report two patients' allergic reactions after HSCT from our center Fondazione Policlinico Universitario A. Gemelli over the past 4 years out of 293 alloHSCT. The subject of the study was approved by Institutional Review Board (IRB) of Fondazione Policlinico Universitario A. Gemelli department of Hematology. The patients underwent TBF conditioning (thiotepa 5 mg/kg on days -6 and -5, busulfan 3.2 mg/kg on days -4, -3, fludarabine 50 mg/m2 -4, -3, -2). For graft failure, the second patient underwent other two transplant after reduced intensity conditioning ('Baltimore' scheme[7] and then cyclophosphamide and fludarabine low dose). Graft versus host disease (GVHD) prophylaxis consisted of cyclosporine A (CSA) 3 mg/kg/daily, cyclophosphamide 50 mg/kg daily for two days post transplant and mycophenolate mofetil. The second patient underwent also thymoglobuline before transplant.

The first patient was a 43-years old woman with a diagnosis of triple negative myelofibrosis with mutation SRSF2, TET2, CUX 1 in NGS analysis (DIPSS-PLUS intermedie 2, MIPSS 70 PLUS high risk), previously treated with aspirin. On July 2021 she underwent (alloHSCT) by a mis-matched unrelated male Donor (UD) and the stem cell source was peripheral blood. She reported nickel hypersensitivity before transplant. Ten

months after transplantation, the patient experienced an episode of urticaria and labial angioedema associated with dyspnoea a few minutes after ingestion of squid; she therefore went to the Emergency Room where she was treated with intravenous methylprednisolone, chlorphenamine and adrenaline with improvement of her symptoms. The patient was subsequently referred to the Allergology and Clinical Immunology Unit of our hospital, where she underwent a food allergy assessment (skin prick test and allergen-specific IgE assay). This revealed a sensitisation to tropomyosin, shrimp, octopus and anisakis simplex. The patient was then instructed about the eating behaviour to follow given her allergies and an adrenalin auto-injector was prescribed. Since then, she has had no further episodes of allergic reactions to food, but she has developed seasonal oculorhinitic symptoms and skin lesions suggestive of atopic dermatitis, which she treats with oral (PO) antihistamine as needed and topical therapy, respectively.

Subsequent investigations showed that the donor had multiple allergies to shellfish, dust mite, mold and hezelnut, without serious problems. The second patient was a 69-years old man affected by Acute Myeloid Leukemia diagnosed in August 2019. He was enrolled in an experimental protocol involving -front line allogeneic transplantation. Therefore, in August 2019 he underwent HSCT by Haplo-identical male donor and the stem cell source was bone marrow. On October 2019 due to graft failure, he underwent to a second HSCT by Haplo-identical female donor and the stem cells source was peripheral blood. During the cytopenic phase, the patient developed a skin rash and underwent a skin biopsy, which showed keratinocyte necrosis with lymphocyte exocytosis and basal vasculopathy with presence of eosinophilic granulocytes, compatible with GVHD. On November 2019, due to a second graft failure, he underwent a third HSCT by male UD and the stem cells source was peripheral blood. The patient reached full donor chimerism after transplant. According to the allergological clinical history, the patient reported only a previous adverse reaction to penicillins. However, after one year from transplant, he developed an eczema with an irrepressible skin itching, poorly responsive to PO antihistamines. Therefore, we referred the patient to the Allergology and Clinical Immunology Unit of our hospital, where he underwent a clinical evaluation. Blood tests revealed an increase in total serum IgE (up to 5203 UI/ml), while the specific serum IgE and the skin prick test were positive for grass pollen, wall pellitory, olive tree, alternaria, aspergillus, cat dander, tropomyosin, latex, anisakis simplex, 2s albumin storage proteins and lipid transfer proteins. The physical examination revealed severe erythema and desquamation on the face and on the upper third of the trunk. He underwent a skin biopsy on an affected

cutaneous area, which documented an epidermal psoriasiform hyperplasia with intense spongiosis, parakeratosis and presence of occasional necrotic keratinocytes and vacuolar degeneration of the dermal-epidermal junction; in the superficial and medium dermis, a lymphomonocytic inflammatory infiltrate was found with a perivascular arrangement and a lichenoid tracts with the presence of interstitial eosinophilic granulocytes, compatible with atopic dermatitis. Interestingly, the donor's medical history was positive for atopic dermatitis, latex allergy and nut allergy.

In 1988, Agosti et al described for the first time the acquisition of a new food allergy after transplantation. He reported transfer of allergen-specific Immunoglobulin(Ig)E-mediated hypersensitivity after allo HSCT [8]. Two different mechanisms were hypothesized: 1) the transfer of allergen-specific B cells that differentiate into IgE plasma cells or the transfer of allergen-specific T cells that help B cells to differentiate into IgE plasma cells; 2) the transfer of hematopoietic cell precursors capable of differentiating into allergy-prone hematolymphatic cells, supporting the differentiation of B cells into IgE plasma cells. In this case, donor and recipient may have different allergens. Khan et al. highlighted five cases that showed transfer of allergy from donor to recipient. In all cases the donor was an identical family member [9]. In 2011, Storek et al described the first case of transfer of allergy from unrelated donor suggesting true transfer rather than development of allergy in a genetically predisposed recipient [10]. In this case, the donor was HLA-matched, hypothesizing that HLA-DR and DQ loci are associated with onset of allergy. However, HLA genes only constitute a smaller fraction of genes associated with allergy [11]. Furthermore, the donor and recipient were not allergic to the same allergens, suggesting a transfer of a hematolymphatic system prone to the development of allergy rather than the transfer of B/T cells specific for certain allergens. In this case, donor and recipient do not have the same clinical manifestations, highlighting that they do not necessarily have the same response [10]. According to Storek, in our cases, the donors were unrelated ones. They were only partially allergic to the same allergens as our patients. In 2016, a German study described a case of peanut allergy after peripheral blood stem cell transplantation (PBSCT) and they considered this case compatible with the concept of allergy transfer via mature specific memory B-cells, highlighting a reactivity model almost identical to that of the donor[12]. T. Mori reported three clinical cases of food allergy in cord blood transplantation (CBT), developed within a year of transplantation, during immunosuppressive therapy, probably due to the dysregulated immune reconstitution[13]. In 2019, a prospective Austrian study analyzed fifty donor-recipient pairs undergoing allogeneic stem cell transplantation; their

findings offer prospective evidence, that showed the risk of transmitting IgE-mediated allergies through HSCT from the donor to the recipient, with an incidence of 1.7%. Furthermore, a significant reduction in allergen-specific IgE responses in patients with pre-existing allergies following HSCT was reported[14]. According to the previous literature, our clinical cases seem to confirm the probable transfer of allergy from donor to recipient, even if it is not possible to prove it. All these cases, indicate the need to transmit information regarding the donor's atopic status and allergies. This information is not only valuable for clinicians caring for these complex patients but also for the patients themselves, as reported in the consensus statement on donor criteria suitability by WBMT [15]. Any health issues in donors that could affect the recipient's daily life should be reported. It's essential to educate patients about this possibility so they can take appropriate precautions to prevent allergic reactions [16]. While the challenge of finding the right donor should not be hindered by these rare occurrences, a complete information about the donor remains essential.

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SP: Writing - review & editing

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References

1. Falkenburg, J. H. F. and Warren, E. H., “Graft versus Leukemia Reactivity after Allogeneic Stem Cell Transplantation,” Biology of Blood and Marrow Transplantation, 2011, vol. 17, no. 1, pp. S33–S38

2. Crocchiolo R, Rombolà G. Human Leucocyte Antigen System and Selection of Unrelated Hematopoietic Stem Cell Donors: Impact of Patient-Donor (Mis)matching and New Challenges with the Current Technologies. J Clin Med. 2023 Jan 13;12(2):646.

3. Bosi A, Bartolozzi B. Safety of bone marrow stem cell donation: a review. Transplant Proc. 2010 Jul-Aug;42(6):2192-4.

4. Ottinger HD, Albert E, Arnold R, Beelen DW, Blasczyk R, Bunjes D et al. German consensus on immunogenetic donor search for transplantation of allogeneic bone marrow and peripheral blood stem cells. Bone Marrow Transplant. 1997 Jul;20(2):101-5.

5. Standard di funzionamento IBMDR, febbraio 2011

6. Atkins D, Malka-Rais J. Food allergy: transfused and transplanted. Curr Allergy Asthma Rep. 2010 Jul;10(4):250-7.

7. Lee CJ, Savani BN, Mohty M et al Haploidentical hematopoietic cell transplantation for adult acute myeloid leukemia: a position statement from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. Haematologica 2017 Nov;102(11):1810-1822.

8. Agosti, J.M., Sprenger, J.D., Lum, L.G., Witherspoon, R.P., Fisher, L.D. et al (1988) Transfer of allergen-specific IgE-mediated hypersensitivity with allogeneic bone marrow transplantation. New England Journal of Medicine, 319, 1623–1628.

9. Khan, F., Hallstrand, T.S., Geddes, M.N., Henderson, W.R. Jr, Storek, J. Is allergic disease curable or transferable with allogeneic hematopoietic cell transplantation? Blood 2009, 113,279–290.

10. Storek J, Vliagoftis H, Grizel A, Lyon AW, Daly A, Khan Fet al. Allergy transfer with hematopoietic cell transplantation from an unrelated donor. Bone Marrow Transplantation 2011, 46, 605-606.

11. Vercelli D. Discovering susceptibility genes for asthma and allergy. Nat Rev Immunol 2008; 8: 169–182.

12. Brauns B , Schön MP ,Wulf G , Mempel M. A lurking threat: transfer of peanut allergy through peripheral blood stem cell transplantation. World Allergy Organ J. 2016 Feb 8:9:3.

13. Mori T, Kato J, Sakurai M, Hashimoto N, Kohashi S, Hashida R et al. New-onset food allergy following cord blood transplantation in adult patients. Bone Marrow Transplantation 2016 Feb;51(2):295-6.

14. Debiasi M, Pichler H, Klinglmüller F, Boztug H, Schmidthaler K, Rech J, Scherer D, Lupinek C, Valenta R, Kacinska-Pfaller E, Geyeregger R, Fritsch G, Haas OA, Peters C, Lion T, Akdis M, Matthes S, Akdis CA, Szépfalusi Z, Eiwegger T. Transfer and loss of allergen-specific responses via stem cell transplantation: A prospective observational study. Allergy 2020 Sep;75(9):2243-2253.

15. Worel N, Buser A , Greinix HT , Hägglund H, Navarro W, Pulsipher MA et al. Suitability Criteria for Adult Related Donors: A Consensus Statement from the Worldwide Network for Blood and Marrow Transplantation Standing Committee on Donor Issues Biol Blood Marrow Transplant. 2015 Dec;21(12):2052-2060.

16. Worel N, Aljurf M , Anthias C, Buser AS, Cody M , Fechter M et al. Suitability of haematopoietic cell donors: updated consensus recommendations from the WBMT standing committee on donor issues. Lancet Haematol. 2022 Aug;9(8):e605-e614.