

Autoimmune Polyglandular Syndrome Type II After Bone Marrow Transplant: Real Transfer or Acceleration of a Programmed Disease?

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Abstract

We report a case of autoimmune polyglandular syndrome type II that developed in an 11-year-old boy with homozygous sickle cell disease after allogeneic bone marrow transplant; the donor was his father, who was human leukocyte antigen identical and had vitiligo. On day 24 after transplant, the patient developed grade 1 acute graft-versus-host disease, which was controlled over a period of 3 months with corticosteroid-induced immunosuppression. Full donor engraftment was documented on day 31 after transplant, and this was further confirmed on days 59, 231, 321, 472, 549, and 720. Three months after transplant, the recipient developed adrenal insufficiency, and at 13 months, he developed vitiligo. Seventeen months after transplant, autoimmune thyroid disease, positive for thyroid peroxidase and thyroglobulin autoantibodies, was diagnosed. At the same time, we identified adrenal insufficiency in the donor. We analyzed a serum sample from the recipient for autoantibody markers for type 1 autoimmune diabetes mellitus. The sample was positive for antiglutamic acid decarboxylase. Antibody against 21-hydroxylase enzyme was also found (261 U/mL; normal value, < 1 U/mL). We conclude that the recipient developed autoimmune polyglandular syndrome type II after bone marrow transplant from his father, who was probably affected by the same syndrome.

Key words: Autoimmune disease transfer, Bone marrow transplant, Cell senescence, Genetic basis

Introduction

Autoimmune polyglandular syndrome type II (APS II) is the combination of chronic autoimmune adrenal insufficiency (ie, Addison disease) and autoimmune thyroid disease, type 1 autoimmune diabetes mellitus (T1D), or both. This syndrome also can be associated with vitiligo; chronic atrophic gastritis, with or without pernicious anemia; hypergonadotropic hypogonadism; and chronic autoimmune hepatitis.¹ We report a case of APS II that developed in a patient with sickle cell disease after allogeneic bone marrow transplant (BMT). The donor was his human leukocyte antigen (HLA)-identical father, who was affected by vitiligo. In this report, we highlight the mechanisms that support development of autoimmune disease (AD) after BMT, based on the timing of clinical and biologic APS II features that occurred in both the donor and recipient.

Case report

An 11-year-old boy with homozygous sickle cell disease received an allograft of 2.8×10^8 nucleated cells/kg from his HLA phenotypically identical father who had been affected by vitiligo for 3 years. The myeloablative regimen consisted of a total dose of busulfan 16 mg/kg, cyclophosphamide 200 mg/kg, and anti-thymocyte globulin 15 mg/kg. For prophylaxis against graft-versus-host disease (GVHD), the patient received intravenous cyclosporine (3 mg/kg/d from day 1 before BMT to day 22 after BMT) followed by 10 months of oral cyclosporine therapy (130 to 90 mg twice a day). On

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day 24 after BMT, the patient developed generalized cutaneous lesions and diarrhea. Grade 1 acute GVHD of the skin and the gastrointestinal tract was diagnosed and controlled over a period of 3 months with corticosteroid-induced immunosuppression. The patient showed *Cytomegalovirus* (CMV) reactivation on day 34 after the BMT, and preemptive ganciclovir treatment was initiated. Full donor engraftment was documented by real-time polymerase chain reaction on day 31 after the BMT, and 100% donor chimerism was further confirmed on days 59, 231, 321, 472, 549, and 720. Because no clinical symptoms of endocrine and/or AD were observed in the recipient before BMT, we did not check for autoimmunity during the pretransplant period.

Three months after the BMT, the patient developed pigmentation on both hands, which generalized to the arms and face 3 weeks later. Laboratory test results showed decreased basal levels of cortisol (55 nmol/L; normal value [NV], 250 to 650 nmol/L), with no increase in response to the adrenocorticotrophic hormone (ACTH) stimulation test. This test involves measuring the serum cortisol concentration before and after injection of synthetic ACTH. In the first step, 0.25 mg synthetic ACTH (corticotrophin [Synacthène]; Ciba-Geigy, Basel, Switzerland) is administered intravenously. At 30 minutes and 60 minutes after ACTH administration, serum is obtained for measuring the cortisol concentration. A maximal cortisol difference between baseline and the highest stimulated cortisol level of less than 193 nmol/L and 248 nmol/L at 30 minutes and 60 minutes is considered a nonresponse, confirming primary adrenal insufficiency.¹

Despite a normal ACTH level (1.73 IU/L NV, < 10.56 IU/L), the above diagnosis was maintained, given that this result was most likely an error owing to serum samples processing problems. Oral hydrocortisone treatment was initiated. Thyroid abnormalities were assessed by analysis of serum-free thyroxine (FT4) and thyrotropin-secreting hormone (TSH). We also checked for thyroid peroxidase antibody (TPO) and thyroglobulin autoantibody (Tg). At that time, no abnormality was found.

Thirteen months after the BMT, at approximately 3 months after termination of cyclosporine, multiple white, depigmented, macular skin lesions of the face, trunk, hands, and feet developed. The lesions

progressed, and vitiligo was diagnosed. Seventeen months after the BMT, autoimmune thyroid disease, with positivity for TPO and Tg autoantibodies, was diagnosed. A high level of TSH (511 mIU/L; NV, 0.17 to 4.0 mIU/L) and a low FT4 level (1.9 pmol/L; NV, 11 to 25 pmol/L) also were found. Diagnosis of hypothyroidism was confirmed, and substitutive treatment with L-thyroxine was initiated. Two years after the BMT, we identified adrenal insufficiency in the donor (cortisol level 113 nmol/L; NV, 250 to 650 nmol/L). The patient experienced no chronic GVHD.

Three years after the BMT, we analyzed a serum sample from the patient for autoantibody markers for T1D (antiglutamic acid decarboxylase [GADA]; antiprotein tyrosine phosphatase [IA-2A]; anti-insulin [IAA]; anti-islet cell antibody [ICA]). Autoantibodies of IgG isotype were assessed by radioimmunoassay for GADA, IA-2A, and IAA, and by enzyme-linked immunosorbent assay for ICA. Positivity for GADA was found (17.1 U/mL; NV, < 1 U/mL). No transglutaminase autoantibody (TGA) was found. Assessment of antibody against 21-hydroxylase enzyme was positive (261 U/mL; NV < 1 U/mL). The father (donor) was screened for the same autoantibodies, and all results were negative.

Discussion

Development of AD after allogeneic^{2, 3} or autologous⁴ BMT has been reported by many researchers. Both organ-specific and systemic ADs have been reported, but the main types described are autoimmune thyroid disease and autoimmune cytopenias.⁵ Several hypotheses have been suggested to explain the occurrence of AD after BMT. These include disease transfer by donor cells (pathogenic lymphocytes or hematopoietic stem cells) or de novo development of AD triggered by BMT.

A variety of factors, such as the type and intensity of conditioning,⁶ total body irradiation,² stem cell source, and drugs used for immunosuppression (by influencing the kinetics of immune recovery),⁷ have been implicated as pre-BMT factors apt to trigger autoimmunity and/or AD. In addition, AD in humans is precipitated after irradiation or other immunosuppressive therapies.⁸ Chronic GVHD and homeostatic peripheral expansion are considered post-BMT factors apt to trigger these processes.

Chronic GVHD has clinical and pathogenic characteristics similar to ADs such as systemic sclerosis, Sjögren syndrome, and autoimmune hepatitis.^{9, 10, 11} It has been reported that development of autoantibodies after allogeneic hematopoietic stem cell transplant (HSCT) is related to chronic GVHD.^{12, 13} Homeostatic peripheral expansion, which constitutes a post-HSCT pathway for T-cell expansion (of either the recipient or donor) develops via rapid cell division of T-cell clones¹⁴ and has been implicated in autoimmunity induction.^{15, 16} The degree of lymphopenia appears to be critical in determining the extent of proliferation.¹⁷ Lymphopenia is one of the major phenomena to occur after allogeneic HSCT and has been associated with a variety of ADs, including insulin-dependent diabetes mellitus,¹⁸ rheumatoid arthritis,¹⁹ systemic lupus erythematosus, Sjögren syndrome, ankylosing spondylitis, and celiac disease.²⁰

Several mechanisms have been proposed for this increased propensity to develop autoimmune reactivity. One hypothesis is that the cytokine milieu associated with lymphopenia may support and augment immune responses, including autoimmunity.²¹ Such conditions may lead to impairment of thymic function, triggering autoreactive T-cell development,^{22, 23} or to homeostatic peripheral expansion of autoreacting effector memory T cells of the donor, which promote autoimmunity development.⁵ However, some models are potentially complicated by the preferential loss of regulatory T cells.¹⁶

Whereas AD can be transferred from donor to recipient, certain severe or refractory ADs can also be resolved after BMT. Some patients who undergo BMT for the treatment of malignant disease achieve long-term remission of coincidental AD.⁹ The strategy is to eradicate preexistent AD by myeloablative conditioning to achieve immunosuppression and replacement or manipulation of hematopoietic stem cells and to induce a graft versus autoimmunity effect.²⁴ Thus, if the basic defect of an AD is within the stem cells, it may be cured in the same way that a hematologic malignancy is eliminated, namely, by allogeneic BMT. If the primary defect is an aberrant immune reaction to an acquired or a self-antigen, tolerance may be acquired in the newly reconstituted immune system by gradual development of donor-derived immunity (immune reconstitution) after allogeneic BMT.⁹ As

mentioned above, this immune reconstitution can be impaired in some situations, leading to autoimmunity.

Autoimmune thyroid disorders are considered to be adoptively transferred in some patients who receive allogeneic HSCT from a donor with an autoimmune thyroid disorder.²⁵ In addition, vitiligo transfer after BMT has been reported; some authors^{26, 27} speculate that vitiligo in the recipient results either from adoptive transfer of pathogenic lymphocytes or because hematopoietic stem cells committed to lymphoid lineages via BMT generate donor-derived autoreactive clones. Evidence of clinical disease in the donor, absence of vitiligo in the recipient before BMT, and complete donor chimerism in recipient at disease onset support such presumptions.²⁶ Genetic predisposition to some HLA haplotypes and the occurrence of chronic GVHD have been mentioned as other causative factors.

In the present patient, the post-BMT period was characterized by the emergence of progressive AD (Figure 1). Adrenal insufficiency appeared respectively at 3 and 24 months after the BMT in the recipient and the donor. Three years after the BMT, anti-21-hydroxylase antibody testing confirmed the autoimmune origin of adrenal insufficiency in the recipient. The presence of GADA in the recipient could indicate a potential triggering of T1D, because this autoantibody constitutes the marker with the highest diagnostic sensitivity for such disease.²⁸ Autoantibodies absence in the donor could indicate a delay in autoantibody occurrence, given that they are known to be a consequence rather than a cause of such ADs. However, Eisenbarth and associates reported that in APS II, distinction of a patient with a single disorder, such as isolated adrenal insufficiency, from a patient with multiple additional autoimmune disorders, depends on several factors.²⁹ Time simply may be one of these factors, because in many patients with adrenal insufficiency, additional disorders develop with age. Given that all APS II components are not always present in each affected member of a given family, the father (donor) may belong to this category.

After BMT, AD transfer has been associated mainly with chronic GVHD.³⁰ Nonetheless, the "cytokine storm" induced by conditioning regimens and acute GVHD persistence for longer than 3 months (as in the present patient) may contribute to central tolerance impairment during immune system

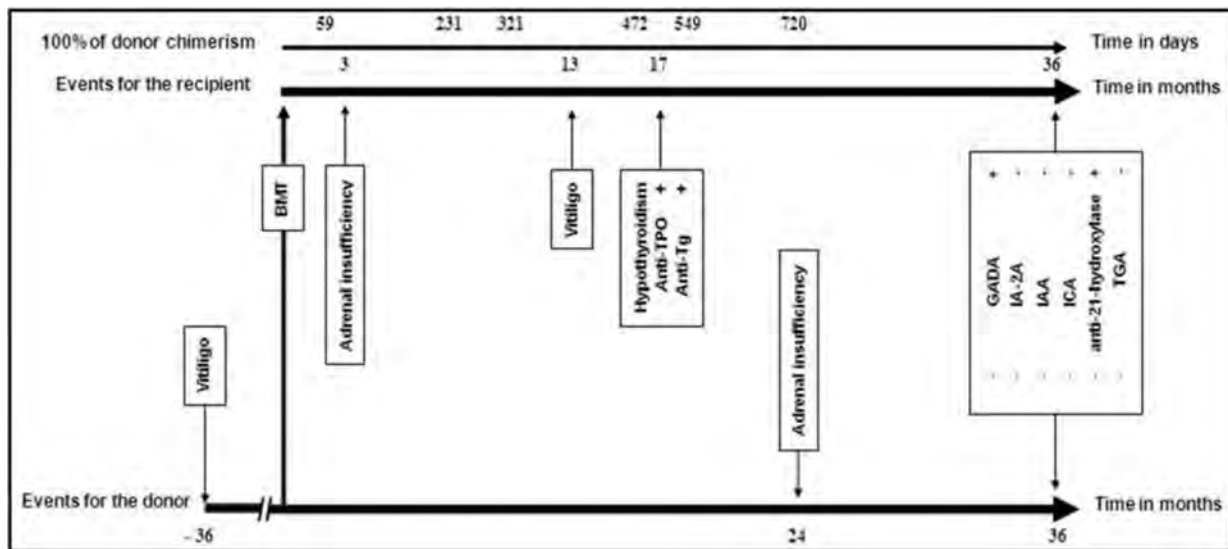


Figure 1. Evolution of clinical symptoms and biologic signs in the recipient and donor.

Abbreviations: anti-21-hydroxylase, anti-21-hydroxylase antibody; Anti-Tg, thyroglobulin autoantibody; Anti-TPO, thyroid peroxidase autoantibody; BMT, bone marrow transplant; GADA, antiglutamic acid decarboxylase; IA-2A, anti-protein tyrosine phosphatase; IAA, anti-insulin; ICA, anti-islet cell antibody; TGA, transglutaminase autoantibody; +, positive; -, negative

reconstitution.³¹ A proinflammatory post-BMT environment and high tissue-specific autoantigen load might be responsible for peripheral immune tolerance loss.³⁰

Genetically, the class II HLA haplotype DR4 (DQB1*0302), which was shared by the recipient and donor in the present study, is strongly linked to APS II.¹³ Phenotypically, environmental factors such as viral infections, may influence APS II diversity.³²

The association of suppressor T-cell telomere shortening with GVHD or viral infection after allogeneic BMT (as in the present patient) represents an attractive possibility.³³ This telomere-dependent pathway activating cell senescence leads to cell and tissue accumulation of autoantigens and may represent a first stimulus for autoimmune responses.³⁴ In addition, cell senescence may contribute to cellular mechanisms leading to impairment of donor regulatory T cells or general deficiency in hematopoietic cells (particularly lymphocytes). These phenomena might accelerate autoimmune responses and the triggering of secondary AD in the recipients (Figure 2).

Reports of autoimmunity transfer after allogeneic BMT should be interpreted with caution because BMT might trigger autoimmune responses. Genetic background represents an obvious causative factor for AD. The distinction between autoimmune and alloimmune organ destruction remains difficult to make. However, early and persistent full donor

chimerism suggests that specific effector donor T cells can trigger disease development. Given that in the context of allogeneic BMT, achievement of full donor chimerism promotes donor rather than host lymphocyte homeostatic expansion,⁵ we can speculate that it could be a real adoptive transfer. However, given that we observed autoimmunity in the recipient and not yet in the donor, we can only speculate that autoimmunity in the recipient was the result of BMT and associated conditions or to a BMT-related hematopoietic cell senescence process, or perhaps to both. Note that the idea of hematopoietic cell senescence is compatible with autoimmunity

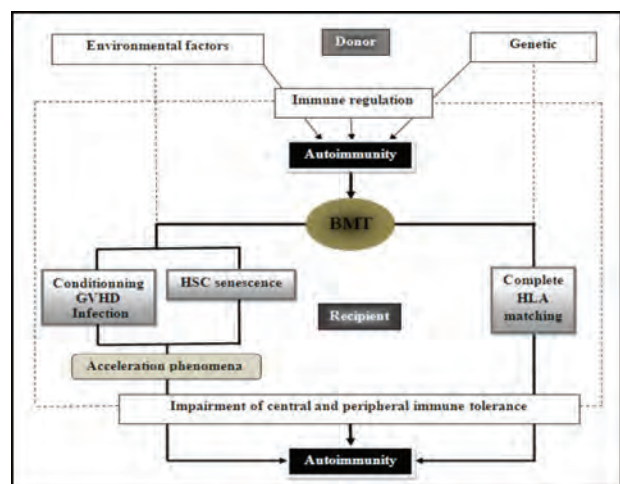


Figure 2. Transfer of an accelerated autoimmune disease.

Abbreviations: BMT, bone marrow transplant; GVHD, graft-versus-host disease; HLA, human leukocyte antigen; HSC, hematopoietic stem cell

transfer because the donor is able to carry this hidden autoimmunity, which is revealed in the recipient by the senescence process.

In conclusion, in conditions of AD strongly linked to HLA haplotype (with complete HLA matching between recipient and donor) and with post-BMT persistent full donor chimerism, a transfer of an accelerated autoimmune response by BMT may be responsible for AD development in the recipient.

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