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Review

Donor skin allograft survival after bone marrow transplantation: Case report and systematic review of the literature☆☆

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Abstract *Background:* We present a case of skin allograft survival in a patient who previously received a bone marrow transplant from the same HLA-matched donor. DNA fingerprinting of skin biopsies showed mixed cellularity originating from the donor and recipient (68% and 32% donor DNA in the allograft skin and the native recipient's skin, respectively). Histologic sections demonstrated both grade 3/4 rejection and graft-versus-host-disease. We have conducted a systematic review in search for other cases of donor skin allograft survival after a bone marrow or hematopoietic stem cell transplantation.

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Methods: All reported cases in English, Spanish, French, and German were captured using the electronic databases. Bibliographies of relevant articles were manually searched.
Results: Nineteen patients (12 females) who received skin allografts from their bone marrow or hematopoietic stem cell donors were identified. Average age was 27.2 years (range: 5 months to 64 years). Skin allografts were used to treat graft-versus-host-disease, Herlitz junctional epidermolysis bullosa, and to test tolerance before a kidney transplantation from the same donor. Eight cases were not receiving immunosuppressive therapy. Allografts survived in all patients. In three patients, skin punch biopsies were taken, and these biopsies demonstrated mixed donor and recipient cellularity. The pathology result is specified in two more cases, with no signs of rejection.
Conclusions: The same donor skin allografts may be a safe option to treat severe cutaneous conditions in recipients of a bone marrow/hematopoietic stem cell transplantation. However, future studies are needed to confirm these results.

Contents

Introduction

Prolonged survival of transplanted organs without immunosuppression has been reported in a small number of kidney or hepatic recipients who received combined bone marrow or enriched hematopoietic cell transplants from the same living donors to achieve durable chimerism.[1-7] Skin is the most immunogenic organ of the body. Achieving its survival without immunosuppression is, therefore, highly challenging.[8,9] We report a case of HLA-matched split-thickness skin allograft (STSA) survival in a patient who previously received a bone marrow transplant (BMT) from the same donor, and we review the literature using a systematic approach to detect other published cases.

Case report

A 17-year-old male presented with a nonhealing 11 cm × 14 cm wound on his back 4 months after an episode of *Escherichiacoli* necrotizing fasciitis. He had a history of Li-Fraumeni syndrome, with the development of multiple malignant tumors including a right pelvic high-grade chondroblastic osteosarcoma; a stage IIIa melanoma in his back with metastasis to a left axillary lymph node; and acute myelogenous leukemia (FAB AML M6). He was the recipient of a BMT from his full (10/10) HLA-matched older brother 16 months before his consultation. However, he required additional chemotherapy and palliative external beam radiation for refractory disease and the appearance of a large retroperitoneal and soft tissue mass in the right pelvis. Since then, he remained transfusion independent, receiving irradiated and leukoreduced blood products. He developed skin graft-versus-host disease (GVHD) that was treated with topical triamcinolone and, for a brief period, with sirolimus. The latter was discontinued because of progression of his extramedullary disease that led to a more expanded field radiation treatment. He then started treatment with decitabine, with no evidence of relapse before consultation.

Upon examination, the patient had generalized lymphedema and multiple wounds in the lower extremities. The wound on his back had been previously treated with a vacuum-assisted closure device and Integra® (Integra®, LifeSciences Corp., Plainsboro, NJ), with no improvement. He had a history of delayed wound healing after other surgeries and refused to have his own skin harvested. Considering this, together with his high level of stable macrochimerism (1% recipient hematopoietic chimerism at the time of surgery), and the fact that his brother was willing to donate a skin allograft, a decision was made to apply an STSA from the latter to cover the wound.

After wound bed preparation with sharp knife debridement and washout, the wound was covered with a 1:1.5 meshed STSA harvested from his brother simultaneously in a contiguous operating room. A vacuum-assisted closure device was placed over it at 75 mmHg with continuous suction. The patient had no postoperative complications and was

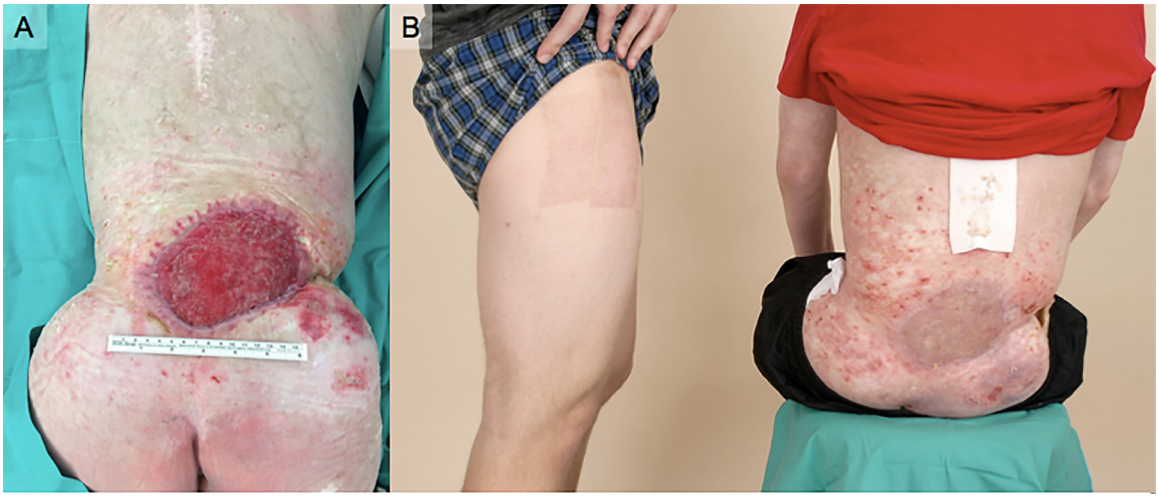


Figure 1A and B Macroscopic appearance of the wounds. (A) Preoperative wound appearance. (B) Postoperative appearance of the donor (left) and recipient (right). The photo was taken 5 months after surgery.

discharged home the same day of surgery. However, because of his GVHD, treatment with systemic sirolimus was restarted 1 month postoperatively, together with dexamethasone and tacrolimus mouthwash. The patient presented a relapse of AML at postoperative month 8. At that time, his GVHD skin lesions had healed completely. Sirolimus was discontinued since then, with no relapse of GVHD, and he started treatment with low-dose prednisone daily for adrenal insufficiency. The patient passed away because of progression of AML at postoperative month 13. No clinical signs of graft rejection were observed during the 13-month period (Figure 1).

Skin punch biopsies were performed 4.5 months after surgery. Histologic sections of the native skin revealed epidermal spongiosis with increased apoptotic keratinocytes and a brisk, predominately lymphocytic infiltrate surrounding hair follicles. Extensively thickened dermal collagen bundles reminiscent of scleroderma were present. These histologic features were consistent with grade 4/4 sclerodermoid GVHD (Figure 2A, B).

Histologic sections from the allograft showed a donor-derived portion of epidermis and superficial dermis overlying dense collagen (Integra) with a proliferation of capillary-sized vessels, foreign material, and hemosiderin at the allograft/native dermis interface (Figure 2C). The epidermis showed mild acanthosis with spongiosis, exocytosis of lymphocytes, and scattered dyskeratotic keratinocytes (Figure 2D). The underlying superficial dermis was mildly edematous with endothelial cell swelling of capillaries, scattered small lymphocytes, macrophages, melanoderma, and hemosiderin deposits. Immunohistochemical staining showed that the lymphocytes were predominantly CD3 + /CD8 + T-cells (CD4: CD8 ratio: 1:3). CD4 highlighted mostly histiocytes, while CD20-positive B-cells were largely absent. CD3 + /CD25 + T-cells were not seen. The presence of dyskeratotic keratinocytes within the allograft was consistent with allograft rejection (grade 3 of 4).

DNA fingerprinting was performed to compare the identities of biopsies taken from the allograft and native skin by using polymerase chain reaction (PCR) amplification followed by fragment length analysis of 15 highly polymorphic STR loci and amelogenin, a sex chromosome-specific locus. The allograft showed peaks matching the native skin in all 16 evaluated loci, thus indicating that these two tissue fragments originated from the same sources (Figure 3). However, seven of the loci in both the allograft and native skin contained more than two peaks that would be expected from tissues originating from a single source (one each of paternal and maternal origin), thereby supporting identical yet chimeric origins of both tissues. Although the peaks at each of these loci were identical in allograft and native tissues, the estimated degree of chimerism differed between the two tissues (estimated using peak areas), with 68% recipient DNA in the native skin and 26% recipient DNA in the allograft.

Methods

Our goal was to identify all full-text, peer-reviewed publications in which recipients of a BMT or a hematopoietic stem cell transplantation (HSCT) had received a skin allograft from the same donor, as well as their outcomes. The PRISMA statement was used as a guideline to perform this review.[10]

The studies were found using a thorough search strategy of the PubMed, Embase, Scopus, Cochrane database of systematic reviews, and Web of Science databases published at any time until September 1, 2017. Both free text words and medical subject heading (MeSH) terms were used. We used the following search terms to retrieve the articles: “Hematopoietic Stem Cell Transplantation,” “Bone Marrow Transplantation,” “Skin Transplantation,” “skin allogr*,” “keratinocyte transpl*,” “skin transpl*.” We limited our search to studies performed in humans that were written in English, Spanish, German, and French. Reference lists of included studies were also searched to identify additional studies of interest.

The identified articles were assessed for inclusion, obtained and agreed upon by two authors. Meeting proceed-

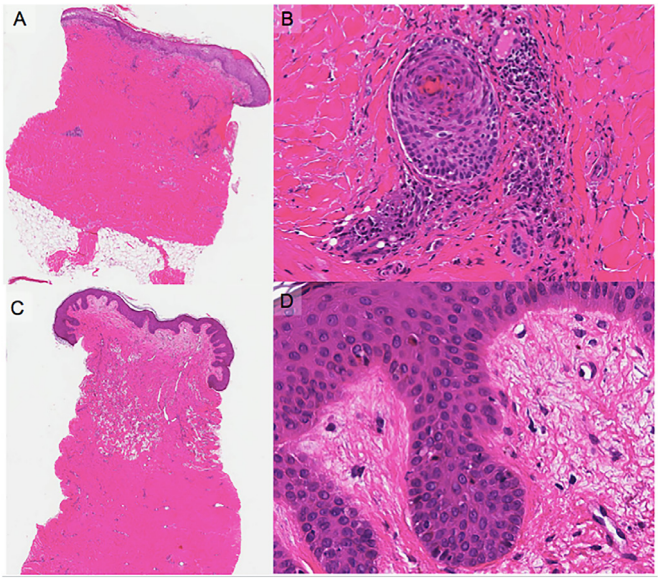


Figure 2A-D Native skin and allograft biopsies. (A,B) "Square punch biopsy" of sclerodermoid graft-versus-host disease (A, H&E, 40X magnification), with dense dermal fibrosis, dense chronic inflammation, and clefting at the dermoepidermal junction (B, H&E, 200X magnification). (C) Allograft with apposition of donor (epidermis and superficial dermis) and recipient-derived (thickened collagen bundles) tissues (H&E, 40X magnification). (D) High-magnification image showing epidermal exocytosis of lymphocytes and dyskeratotic (apoptotic) keratinocytes, consistent with severe acute rejection (H&E, 400X magnification).

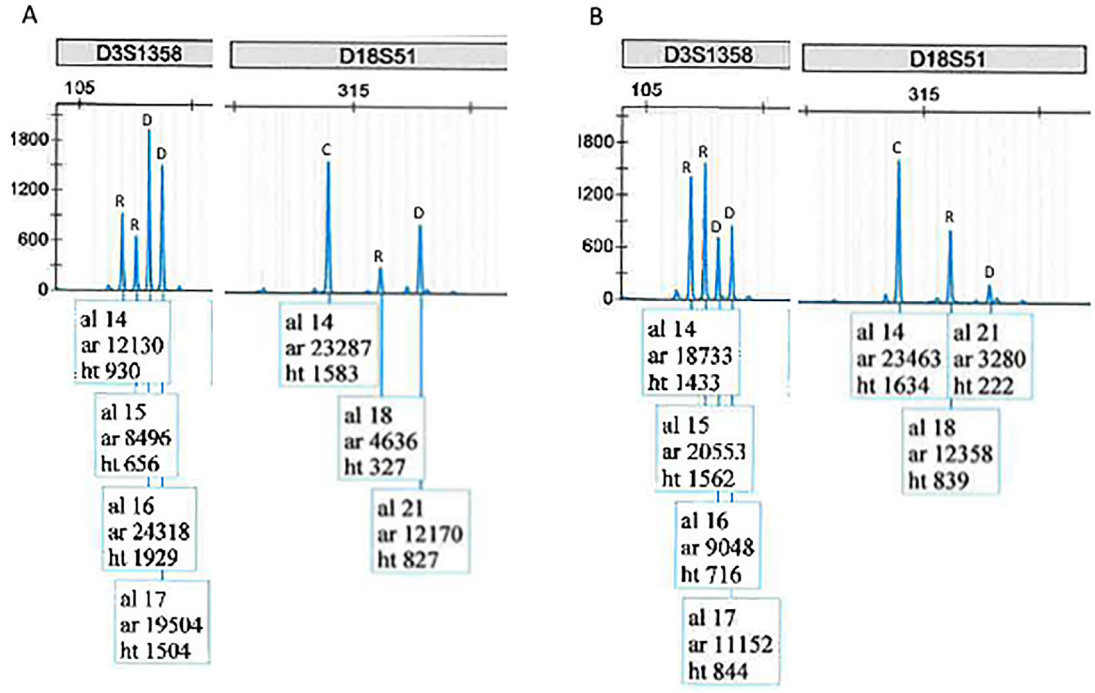


Figure 3 Representative DNA fingerprinting (DNAFP) results of two informative short tandem repeat (STR) loci (D3S1358 and D18S51) using known recipient and donor STR profiles. The presence of STR variants at multiple loci indicates a mixed-source DNA (recipient and donor). Results were reported as percent recipient DNA. (A) Allograft biopsy DNAFP results. Relative peak heights indicate predominantly donor DNA (D peaks > R peaks). Calculated percent recipient DNA using the area under the curve of informative alleles was 32.0% (D3S1358) and 27.6% (D18S51). B. Native skin biopsy DNAFP results. Relative peak heights indicate predominately recipient DNA. Percent recipient DNA was 66.0% (D3S1358) and 79.0% (D18S51). NOTE: the percent recipient DNA is calculated by averaging the results from all informative loci.
Al, allele; ar, area; ht, height; R, recipient allele; D, donor allele; S, shared allele.

ings, expert opinions, book chapters, or reviews were excluded. Inclusion criteria were articles reporting prospective and retrospective studies of patients of any age who had undergone HSCT/BMT, and a skin allograft from the same donor. Outcomes to measure included tolerance of the allograft, success in reconstructing the defect for which the allograft had been used, and complications related to the procedure. Autografts and third-party allografts were used as comparators if they were also applied to these patients.

After running the term search strategy, duplicate articles were removed. Articles for which the abstract met the inclusion criteria, or was lacking information, were obtained as full-text articles. Next, full-text articles were reviewed in accordance with the inclusion criteria. Only the data of patients with objective information were included in the quantitative assessment. If there were multiple publications by the same author (group) of the same patients, the studies were combined. Articles were graded on quality of evidence using the American Society of Plastic Surgeons Levels of Evidence Rating Scale.[11]

Results

We examined 256 papers and identified 22 articles that met our criteria. The search strategy and flow diagram are presented using the PRISMA guidelines[10] (Figure 1). Results focused on the demographic characteristics of the patient and the donor, degree of chimerism, immunosuppressive therapy (IST), indications and characteristics of the skin allograft, and outcomes.

The results of these 22 papers are summarized in Table 2.[10,12–33] All the studies selected were case reports or letters to the editor containing case reports (ASPS level of evidence V[11]) published between 1963 and 2017. They included 19 patients who received skin allografts from their BMT/HSCT donors. The papers were published by different groups from Europe, Asia, and North America. Only one group published two different cases.

Demographics

Demographic data are summarized in Table 2. In all the cases, the donors were family members. In 15 patients, the donor was an HLA-identical sibling, and in two patients a haploidentical parent. In one individual, the donor was a sibling whose HLA typing is not stated. One patient received blood and bone marrow from his parents and four siblings and accepted the donor (a sibling) with the nearest histocompatibility test result, but their HLA is not specified.

Hematopoietic chimerism

Information regarding chimerism was available for 12 patients (five had full donor chimerism, one had 98 to 99% donor chimerism, and one had 50% donor chimerism). Four papers reported that the patient's blood type or red blood cell phenotype turned into the donor's phenotype after the transplantation. Almost 100% of the erythrocytes of the patient who received the blood and bone marrow from six different donors had one male donor's phenotype, but 0–4% of the leukocytes were produced from cells of a female donor.

Immunosuppressive therapy

The different IST regimens are summarized in Table 2. At the moment of transplantation, 10 patients continued receiving IST for GVHD prevention or treatment.

Procedure indications and technique

Indications for skin allograft included chronic cutaneous GVHD or its sequelae ($n = 13$), tolerance test before a kidney transplantation from the same donor ($n = 4$), determination of the donor of the engrafted hematopoietic cells in a case with six different BMT donors ($n = 1$), and to overcome the immune barrier and allow for skin exchange in a 5-month-old girl with H-JEB.

Most individuals received conventional STSA or full-thickness skin allografts (FTSA). In two cases (the same author), the skin allografts were placed over glycerolized allogeneic skin. Cultured donor keratinocytes were used in two cases. The size of the grafted defects was very variable, ranging from 1×1 cm ulcers to 80% of the total body surface area.

Outcomes

Average graft follow-up time of the cases was 2.3 years (range: 30 days to 6 years). All the cases showed survival of the BMT/HSCT donor's skin allografts. In one of the six patients who also received autografts, the autograft skin darkened over the areas of GVHD ulcer, whereas all the areas with skin allografts maintained a pink color. Allografts from third-party donors were rejected in the three patients who received them.

In five cases, a dramatic improvement or resolution of the skin GVHD after the procedure is reported. This allowed to stop systemic IST in two cases and to reduce it to a low dose of prednisone daily in another one. Three cases in which the skin allograft was used to test tolerance received a kidney transplant from the same donor. The kidney survived without IST in the three of them.

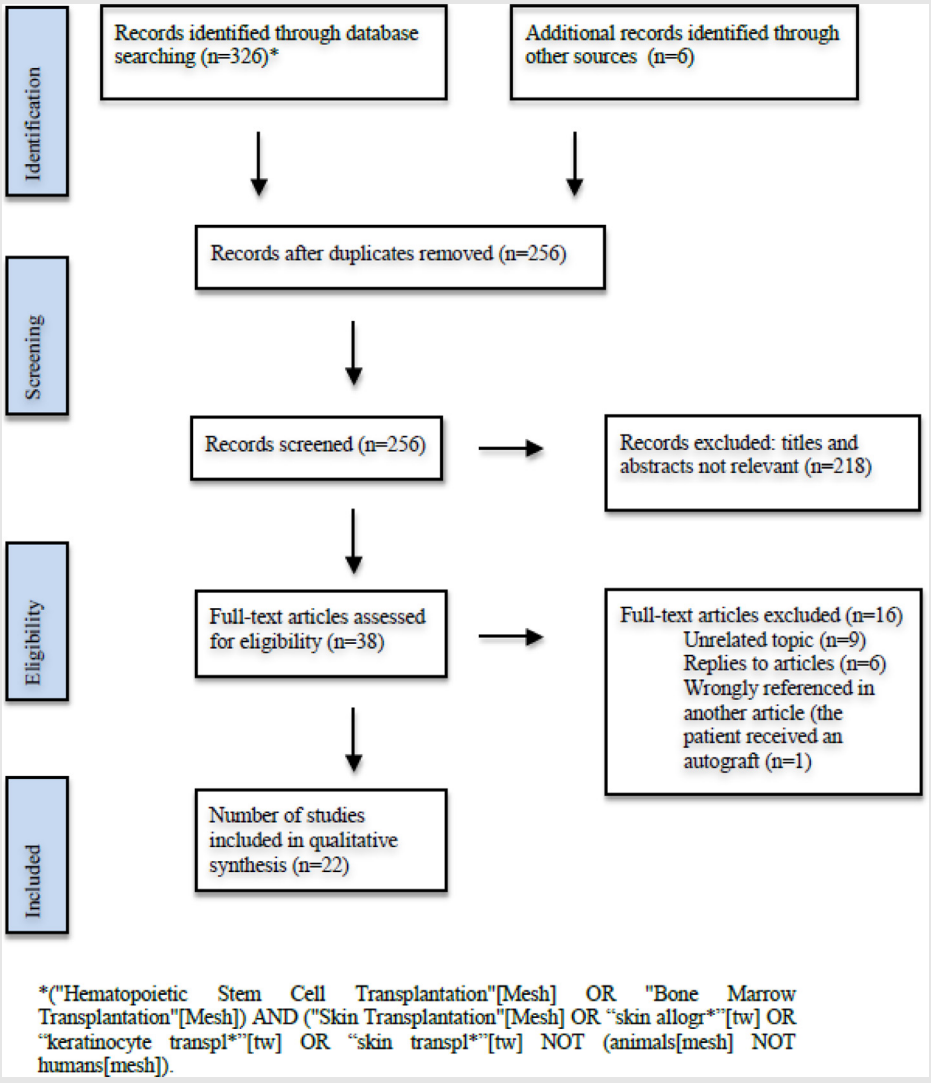
Two patients died because of infections that were unrelated to the skin graft (herpes zoster meningoencephalitis and sepsis). There were no postoperative complications related to the skin grafting procedure.

Punch biopsies of the allograft skin were obtained in five patients. The pathology result is specified in two cases, with no signs of rejection. Y-chromosomes were detected in the skin specimen in two female patients with male donors. Chimerism analysis was performed in one patient, thus demonstrating 20% donor and 80% recipient DNA 6 years after the procedure.

Discussion

BMT/HSCT induced prolonged survival of skin grafts from the same donor in at least 20 patients worldwide, and in

Table 1 Search strategy using PRISMA flowchart.



some cases without immunosuppression. Prolonged survival of solid organ kidney and liver transplantations without immunosuppression has also been reported in a small number of human recipients of solid organ transplantation with hematopoietic chimerism, although this survival was not achieved in all the patients.[1-7]

Seven decades ago, tolerance was defined as nonresponsiveness to donor antigens, after observing that Freemartin cattle (fraternal twins sharing placental circulation) were chimeric and tolerant to skin grafts from each other.[34,35] The subsequent demonstration of antigen-specific regulation as a mechanism of tolerance led to an updated definition of tolerance as the specific absence of a destructive immune response to a transplanted tissue in the absence of immune suppression.[36] Operational tolerance, defined in the context of liver transplantation, is the successful weaning from immunosuppression and maintenance of stable function for greater than 1 year.[37,38] Prope tolerance is defined as minimization of maintenance immunosuppression, typically following induction therapy with a depleting agent such as alemtuzumab.[39,40] Defining tolerance in the context of bone marrow transplantation is further complicated by the degree of chimerism achieved. In a patient experiencing full-donor chimerism following BMT who subsequently received a tissue or organ transplant from the same donor, it should stand to reason that the transplanted tissue (donor) will be recognized as "self" by the patient's (now donor derived) lymphocytes and therefore not rejected.[15] We do not know whether this is truly an induction of transplant tolerance or just preservation of donor self-tolerance in a new host.

Donor skin transplantation in BMT/HSCT patients was first attempted in the 1960s, when Mathe et al started grafting allogeneic hematopoietic cells from multiple donors, following total body irradiation (TBI), to treat acute leukemia. Skin allografts from different donors were then used to determine who was the donor whose cells had engrafted.[27-29]

Based on the fact that it is difficult to assure that 100% of the recipient immune system has been eradicated and that the presence of donor-type microchimerism does

Table 2 Summary of case reports.

Authors	Age gender diagnosis	Transplant type donor	Hematopoietic chimerism	Conditioning regimen	IST before skin graft	IST after skin graft	Allograft type	Defect cause size location	Clinical tolerance DNA/Histology	Outcome	Graft follow-up time
Amendola et al. [12]	30 y M AML	BMT HLA-identical sibling	NS	RTX + BTZ	Cy + SLM	Cy + SLM	STSA	GVHD Diameter 10 cm Thigh	Y	Wound healed	8 w
Ammer et al. [13]	29 y F Flt-3 + AML	HSCT HLA-identical sister	Full donor	Myeloablative (NS).	PSL, TAC, ETN, DAC, ATG, MMF, RTX, EVE, MTX	PSL + MMF + MTX, tapered to MMF, then no IS.	STSA (meshed 1:1.5)	GVHD 12 × 17 cm Scalp	Y	Wound healed D/c IST	29 m
Baumeister et al.[14]	20 y M AML	BMT HLA-identical brother	NS	BCNU, Ara-C, Cy + TBI (9,4 Gy)	MTX. PSL + AZA	PSL + AZA. Then, PSL + CsA.	STSA	GVHD NS Both legs	Y	Wound healed No new ulcers.	4 y
Berg et al.[15]	49 y F FM-NHL	PBSC HLA-identical sister	Full donor	FLU + TBI (2 Gy)	CsA + PSL + MMF	CsA + MMF. Then INX was added. Afterwards, only PSL.	STSA (meshed 1:1.5)	GVHD 12 × 15 cm^{2} Scalp	Y	Wound healed Reduced IST	3 y
Caffee and Miller[16]	17 y M Aplastic anemia	BMT HLA-identical sister	NS	NS	NS	PSL + AZA.	NS type of skin allograft	GVHD NS NS	Y allografts of 2 other donors rejected	Wound (allograft and autograft) healed	2 m
Crocchiolo et al.[17,18]	34 F AML	BMT HLA-identical sister	Full donor	Cy + TBI (12 Gy)	CsA + MTX. Steroids + RTX + IM + MTX + ECP	RTX + IM + EVE + ECP + MTX. Afterwards, no IS.	1:1.5 meshed glycerolized-killed skin allografts, and cultured donor keratinocytes.	GVHD 15% TBSA Back, groin, and flanks	Y Mixed-skin chimerism (20% donor, 80% recipient)	Wound healed D/c IST.	6 y
Elias et al.[19]	14 y F AML	BMT HLA-identical brother	NS	Ara-C, + L-PAM + TBI	Steroids + AZA + CsA	No	FTSA	GVHD sequelae NS Bilateral popliteal region	Y	Wound healed	4 y
Helg et al.[20]	26 y F Early-B ALL	BMT HLA-identical brother	Full donor	Ara-C + Cy, mPSL, TBI (1200 cGy), ex-vivo BM graft T-cell depletion with MoAb CD52 + autologous complement	CsA 35 days. VRE for HUS	No	FTSA STSA	Tolerance testing NS NS	Y	Tolerance to donor's kidney	2 y

(*continued on next page*)

Table 2 (*continued*)

Authors	Age gender diagnosis	Transplant type donor	Hematopoietic chimerism	Conditioning regimen	IST before skin graft	IST after skin graft	Allograft type	Defect cause size location	Clinical tolerance DNA/Histology	Outcome	Graft follow-up time
Kamei et al.[21]	47 y F APML	BMT Sibling, HLA NS	NS	Cy + PSL	PSL + AZA	PSL + AZA	STSA	GvHD 2 × 3 cm Right medial maleolus	Y	Wound (allograft and autograft) healed	18 m
Knobler et al.[22]	16 y M Aplastic anemia	BMT HLA-identical brother	Donor red blood cell phenotype and isoenzyme patterns	TLI (2400 rad) + Cy	PDN + AZA	AZA + PDN	STSA	GVHD NS Trunk and extremities	Y	Wound healed Autografts darkened	NS
Kondo et al.[23]	35 y F CML	BMT HLA-identical brother	NS	Bu + Cy	PSL + CyA. mPSL + Gus added	PSL + CsA	NS type of skin allograft	GvHD 2 × 4, 2 × 2 and 1 × 1 cm Left foot	Y	Wounds healed	17 m
Kopp et al.[24,25]	38 y F CML	BMT HLA-identical brother	Hematopoietic chimerism, NS degree	NS	INF-α (leukemic relapse). IST (agents NS).	No	STSA and glycerolized allogeneic skin	GVHD 5% TBSA Trunk	Y-chromosomes in skin	Wound healed	Months (number NS)
	5 m F H-JEB	CD34 + PBSC HLA-haploidentical father	NS	Cy + Bu + L-PAM + ALG	Infusion of donor granulocytes. Rest, NS.	NS	STSA and glycerolized allogeneic skin	Epidermolysis 80% TBSA Trunk, arms, leg, gluteal regions	Y-chromosomes in the skin	Skin healed Conditioning possibly enhanced skin loss Death (sepsis)	$\geq$ 67 d
Mache et al.[26,34,35]	11 y F Aplastic anemia	CD34 + PBSC HLA-haploidentical mother	98-99% donor	ATG + Cy + FLU	No	No	FTSA	Tolerance test NS (small) Groins	Y	Kidney transplant not performed	23 m
Mathé et al.[27-29]	26 y M ALL	Blood and BMT 6 donors - parents and 4 siblings. Accepted donor with nearest histo-compatibility test result	$\approx$100% erythrocytes had one male donor's phenotype, 0-4% leukocytes from a female donor	AZA + TBI (800 rad) + EACA + cortisone	Donor-specific leukocytes (antileukemic effect). Hydrocortisone	No	NS type of skin allograft	Tolerance test. NS size NS location	Only autograft and allograft of 1 donor tolerated	BMT donor identified. Death (herpes zoster meningoen-cephalitis).	12 m

(*continued on next page*)

Table 2 (*continued*)

Authors	Age gender diagnosis	Transplant type donor	Hematopoietic chimerism	Conditioning regimen	IST before skin graft	IST after skin graft	Allograft type	Defect cause size location	Clinical tolerance DNA/Histology	Outcome	Graft follow-up time
Milner et al[30]	23 y F ALL, CML	HSCT HLA-identical sister	50% mixed chimerism	Bu + FLU	MTX + TAC	MTX + TAC	Cultured donor keratinocytes	GVHD 1700 cm^2 Head and back	Y	Wound healed	30 d
Ravanan et al.[31,37,47]	64 y M CML	BMT HLA-identical sister	Full donor	NS	Steroids + Cy Donor lymphocyte infusion for relapse	No	FTSA	Tolerance test. NS size NS location	Y No signs of rejection in histology.	Tolerance to donor's kidney	30 m
Sellers et al.[32]	37 y F CML 34 y	BMT HLA-identical sister	Donor's blood type	TBI + splenectomy + chemotherapy (NS)	CyA + MTX	No	FTSA	Tolerance test. NS size NS location GVHD	Y No signs of rejection in histology.	Tolerance to donor's kidney	6 y
Storb et al[33]	M Aplastic anemia	BMT HLA-identical sibling	Donor's RBC phenotype	Cy	ATG	No	FTSG STSG	NS size NS location	Y A different donor's allograft rejected.	Wound healed	2 y

AML - acute myelogenous anemia, ALG - anti-T lymphocyte globulin, ALL - acute lymphoblastic leukemia, APML - acute promyelocytic leukemia, Ara-C - Cytarabine, ATG - antithymocyte globulin, AZA- azathioprine, BCNU - Bischlorethylnitrosurea, BM - bone marrow, BMT - bone marrow transplantation, BTZ - bortezomib, Bu - busulfan, CML - chronic myelogenous anemia, CsA - cyclosporine, Cy - cyclophosphamide, DAC - daclizumab, D/c - discontinue, EACA - aminocaproic acid, ECP - extracorporeal photopheresis, ETN - etanercept, EVE - everolimus, F - female, FISH - fluorescence in situ hybridization, FLU - fludarabine, FM-NHL - follicular mixed non-Hodgkin's lymphoma, FTSA - full-thickness skin allograft, Gus - gusperimus, GVHD - chronic graft-versus-host-disease, H-JEB - Herlitz junctional epidermolysis bullosa, HSCT - hematopoietic stem cell transplantation (not specified whether bone marrow or peripheral), HUS - Hemolytic uremic syndrome, IM - imatinib, INF-α - Interferon-alpha, INX - infliximab, IST - immunosuppressive therapy, L-PAM - melphalan, M - male, m - months, MMF - mycophenolate mofetil, MoAb CD52 - alemtuzumab (Campath-1 monoclonal antibody), mPSL - methylprednisolone, MTX - methotrexate, NS - not specified, PBSC - peripheral blood stem cells, PDN - prednisone, PSL - prednisolone, RTX - rituximab, SLM - sirolimus, STSA - split-thickness skin allograft, TBI - total body irradiation, TAC - tacrolimus, TBSA - total body surface area, w - weeks, TLI - total lymphoid irradiation, VCR - vincristine, Y - yes, y - years.

not uniformly exclude graft rejection,[26,31,41] skin allografts have also been used to demonstrate the acceptance of the BMT/HSCT donor's tissue before performing a kidney transplant.[26,32] This is, however, controversial. First, there is a possibility of split tolerance (tolerance of the organ allograft but rejection of the skin allograft) in case of mixed hematopoietic chimerism.[42,43] Second, tolerance of a skin graft would not assure tolerance of a kidney if minor antigens expressed by the skin differed from those by the kidney. Furthermore, if a minor antigen was shared by the skin and kidney, but not bone marrow cells, a skin graft might sensitize the host before the kidney transplant.[44] Finally, skin grafting cannot be used reliably to predict long-term allograft survival or chronic rejection, which is the most common cause of late allograft failure.[45] In spite of these concerns, the kidney was transplanted in three cases and was tolerated without IST with follow-up times of up to 6 years.[32]

In the majority of cases, skin allografts have been used successfully to treat chronic cutaneous GVHD[12-18,21-24,28,33] or its sequelae.[19] Moreover, some authors reported a dramatic improvement in the GVHD allowing to taper[15] and even stop IST in their patients.[13,17] A possible explanation is that the skin-derived precursor cells from the donor's skin allograft had tolerogenic properties that would have induced remission of the GVHD.[17]

At least nine of the cases identified, including our own case, were not receiving IST during transplantation. There are other reports of skin allograft take without IST in patients who received intermingled parental skin allograft and autografts,[46,47] or unrelated donor allografts,[48,49] to treat burn injuries. However, in most cases, no donor cells persisted during the course of time in the epidermis of these allografts, thereby suggesting that creeping substitution of the allograft by recipient cells took place.[46,48] In one case, the biopsies demonstrated donor and recipient cells 221 days after surgery, but the allograft was rejected after obtaining the skin biopsy.[49]

STSAs have survived for more than 12 years in patients who underwent renal transplantation from the same donors. DNA tissue typing in these cases demonstrated both donor and recipient cells in skin allograft specimens from patients under IST. However, DNA tissue typing performed on one patient after discontinuing IST revealed only autogenous cells in the allograft specimen. A reasonable hypothesis is that the host immune system rejected the transplanted donor skin cells, and donor cells repopulated the donor skin.[50]

The presence of donor cells in punch biopsies of the skin allograft was assessed in three BMT/HSCT patients.[17,18,24,25] In two female patients with male donors, X- and Y-chromosomes were demonstrated by fluorescence in situ hybridization[24] and quantitative PCR (one Y chromosome per cell equivalent in the epidermis),[25] respectively, indicating stable integration of the donor's skin. In another case, chimerism analysis demonstrated mixed chimerism (20% donor, 80% recipient) on the skin graft 6 years after the procedure.[17]

In our case, DNA fingerprinting analysis demonstrated 32% donor DNA in the recipient's native skin, in contrast to 74% donor DNA in the healed allograft. This is consistent with the notion that the allograft is a donor-derived tissue. The 26% recipient DNA in the graft most likely represents recipient-derived CD3-positive T cells; however, other sources of recipient DNA, such as keratinocytes, endothelial cells, and other antigen-presenting cells, may also contribute. Our patient's histopathologic findings were consistent with a graft rejection. The reasons why this did not correlate with clinical signs of rejection are unknown to us. One potential theory is that this biopsy represents only a static snapshot in time, in which we are witnessing the body and allograft in what is actually a constant dynamic flux balancing between tolerance and rejection in the embattled chimeric state. The histopathology is only reported in two other cases in the literature and, conversely, there were no signs of rejection.[31,32]

The donor was a full-HLA matched sibling in 19 cases, and a haploidentical parent in two.[25,26] It is unclear whether an HLA mismatch or a nonrelative donor would have altered their outcomes. In patients with severe burns, skin allografts with higher HLA compatibility have longer survival times.[51] However, permanent tolerance of skin allografts has been demonstrated across major histocompatibility barriers in animal models.[9,52,53]

Most individuals were treated with STSAs or FTSAs. Cultured keratinocytes were used in two patients,[18,30] in one case after providing a new dermal layer with glycerolized-killed allografts.[18] This is an interesting approach to consider for large defects, as it limits the amount of tissue harvested from the donors.

An important limitation of our study is that all the papers identified in our review were case reports. There is an important risk of publication bias, as cases in which this procedure was unsuccessful may have not been published. Additionally, studies of this type are not appropriate to generalize, as there is no possibility to establish cause–effect relationship, they have a retrospective design, and there is a danger of overinterpretation.

Another limitation is that overall immunocompetence of the patients was not evaluated in most cases, thereby leading to the question as to whether or not donor-specific tolerance was induced.[45] However, all the patients who did receive third-party skin allografts rejected them.[16,27-29,33] Furthermore, in another patient, in vitro mixed lymphocyte reaction documented unresponsiveness to donor's lymphocytes but reacted normally to third-party lymphocytes.[22]

Finally, although none of the patients had any complication related to the allograft, the population susceptible of needing this type of procedure usually has a poor baseline condition. Two patients died during their follow-up. One was a child with H-JEB, with a clinical course complicated by multiple infections.[25] The other had undergone a BMT after TBI and died of herpes zoster meningoencephalitis.[27-29]

In conclusion, allogeneic skin grafting from the same BMT/HSCT donor may be a safe option to treat severe cutaneous GVHD, large skin defects, life-threatening diseases of the skin, burns, trauma, or cancer surgery in these patients. However, because of the low level of evidence of case reports, prospective studies and clinical trials are needed in the future to confirm these results.

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