Leukemia Research Reports 9 (2018) 72–75

Contents lists available at ScienceDirect

Leukemia Research Reports

journal homepage: www.elsevier.com/locate/lrr

Sezary syndrome manifesting as posttransplant lymphoproliferative disorder

Thanh-Phuong Afiat[a], Xiaohui Zhang[b], Hailing Zhang[b], Ernesto Ayala[c], Ling Zhang[b], Lubomir Sokol[d,*]

[a] Department of Internal Medicine, College of Medicine, University of South Florida, 12902 USF Magnolia Drive, Tampa, FL 33612, USA
[b] Department of Hematopathology and Laboratory Medicine, Moffitt Cancer Center, Tampa, FL, USA
[c] Department of Blood and Marrow Transplant, Moffitt Cancer Center, Tampa, FL, USA
[d] Department of Malignant Hematology, Moffitt Cancer Center, Tampa, FL, USA

ABSTRACT

Posttransplant lymphoproliferative disorders (PTLDs) of T-cell orgin are rare biologically heterogeneous diseases of mature lymphoid cells manifesting in immunosuppressed patients. Only a few cases of mycosis fungoides diagnosed post allogeneic hematopoietic cell transplant (alloHSCT) have been described so far. We present a patient with myelodysplastic syndrome (MDS) post matched unrelated donor alloHSCT who was on long-term immunosuppressive therapy due to graft versus host disease. Three years after an alloHSCT, she developed generalized erythroderma and peripheral blood lymphocytosis. Both skin biopsy and peripheral blood flow cytometry revealed atypical CD4+ T-cell population consistent with diagnosis of Sezary syndrome. Chimerism studies revealed 100% donor engraftment. Therapy with extracorporeal photopheresis resulted in complete response in blood and skin.

1. Background

The late complications of alloHSCT include secondary malignancies such as post-transplant lymphoproliferative disorder (PTLD), solid cancers and acute myeloid leukemia/myelodysplastic syndrome (AML/MDS). Among these, PTLD is the most common and typically manifests within six months to one year post-transplant. The majority of PTLDs (>90%) originate from Epstein-Barr virus (EBV) infected B-cells, are donor-derived and occur in the setting of significant immunosuppression leading to decreased immune surveillance of infected B-cells. Other risk factors include the degree of T-cell depleted grafts, host genetic factors, DNA damage secondary to chemotherapy and/or radiation. In contrast, EBV-negative PTLDs typically present more than 1 year after transplant and are non-B-cell in origin [1]. While it has been recognized that up to 15% of PTLDs after solid organ transplant are T-cell in origin, there has only been a handful of reports of T-cell lymphoma and even fewer reports of cutaneous T-cell lymphoma (CTCL) following alloHSCT [2]. Here, we report, a rare case of Sezary syndrome (SS) following alloHSCT from an HLA-matched unrelated donor.

2. Case presentation

Seventy-three year-old female with history of high risk MDS was treated with 5-azacitidine, followed by conditioning with busulfan and fludarabine and alloHSCT from a matched unrelated donor with achievement of complete remission (CR). She was on tacrolimus and sirolimus for immunosuppression. Her post-transplant course was complicated with chronic graft versus host disease (cGVHD).

Approximately three years after alloHSCT, she developed a generalized confluent erythematous rash that was pruritic and continued to worsen. Other than chronic dry eyes and mouth secondary to cGVHD, she was asymptomatic. She was seen by a local dermatologist and underwent skin biopsy. The diagnosis of dermatitis possibly due to drug eruption was made and she was treated with 0.1% triamcinolone cream with minimal improvement. Labs at three months after rash manifestation showed leukocytosis of 12.75 k/uL with 1.66 K/uL atypical lymphocytes, elevated LDH of 261 U/L, hyperglycemia of 258 mg/dL and mildly elevated creatinine of 1.2 mg/dL. Peripheral blood flow cytometry revealed cytologically and phenotypically atypical lymphocytes (Fig. 1A), which prompted additional work up.

Subsequent bone marrow biopsy revealed atypical lymphocytic infiltrate cytologically and phenotypically consistent with mature CD4+ T-cells with decreased expression of CD2, CD3, dim to loss of CD7, loss of CD26 and elevated CD4:CD8 ratio of 19.4 (Fig. 1B, E). Bone marrow was normocellular with trilineage hematopoiesis, and no evidence of recurrent MDS. Sorted CD3(+) and CD33(+) chimerism studies in peripheral blood and unsorted bone marrow chimerism revealed 100% donor engraftment suggesting that malignant T-cell population was

* Corresponding author.
E-mail address: Lubomir.Sokol@Moffitt.Org (L. Sokol).

https://doi.org/10.1016/j.lrr.2018.04.006
Received 7 March 2018; Received in revised form 17 April 2018; Accepted 30 April 2018
Available online 01 May 2018

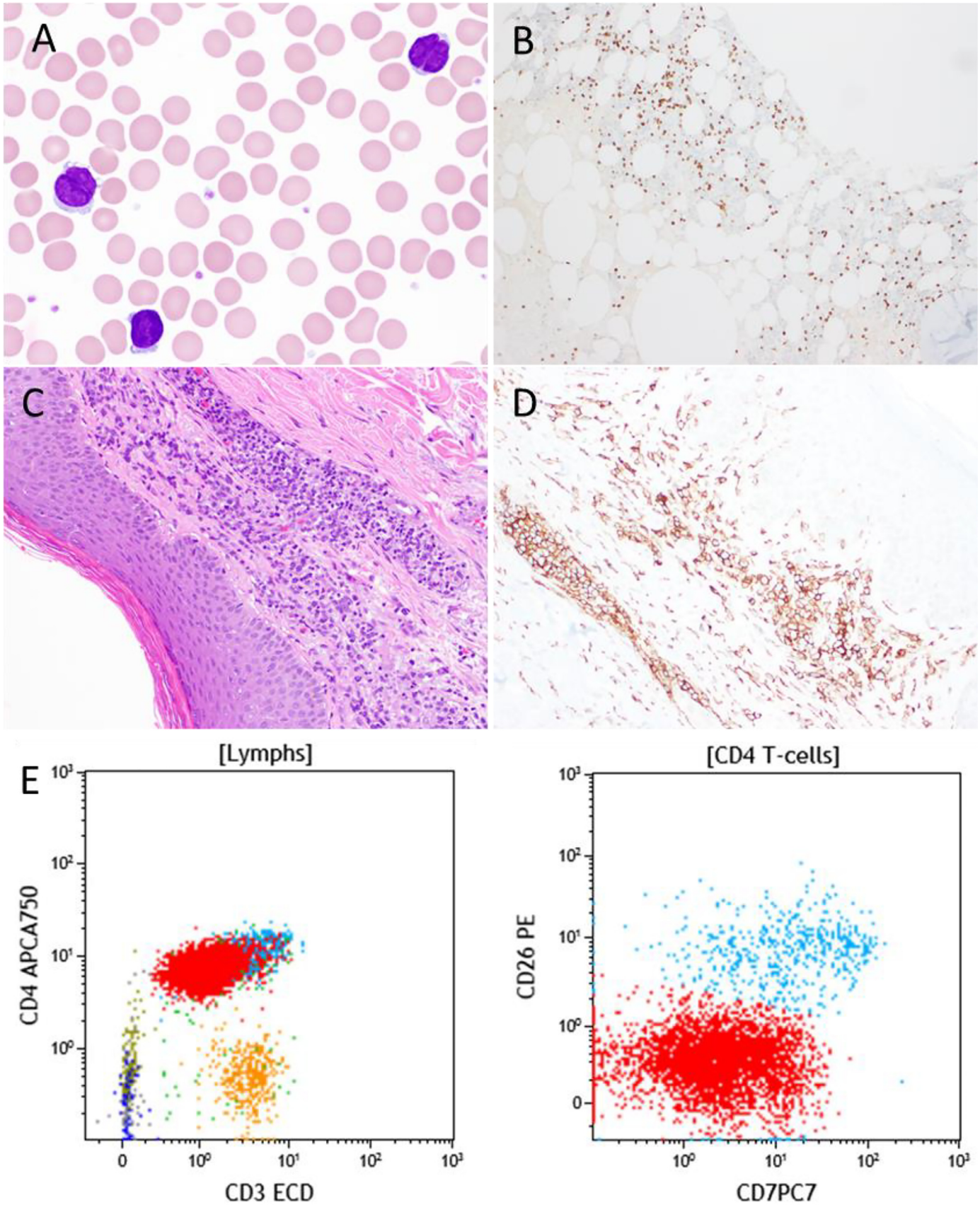

Fig. 1. A. Circulating atypical lymphocytes with irregular nuclear contours in the peripheral blood. 1B. Slightly increased interstitial CD3+ T-cells in the bone marrow biopsy (CD3 immunohistochemical stain, ×100). 1C. Skin biopsy showing superficial dermal atypical lymphocytic infiltrate (H&E stain, ×200). 1D. The dermal atypical lymphocytes are mainly CD4+ cells (CD4 immunohistochemical stain, ×200). 1E. Flow cytometry performed on the peripheral blood showed an atypical CD4+ T-cell population, which decreased CD3 expression, dim CD7 and loss of CD26.

Table 1
Reported cases of MF/SS post allogeneic hematopoietic stem cell transplant.

Reference	Original diagnosis	Immunosuppresant	Type of donor	Time of rash development from alloHSCT	Rash presentation	Skin biopsy findings	EBV	TCR gene rearrangement	Chimerism	Other	Diagnosis	Treatment
Santos-Briz et al. [3]	Mantle cell lymphoma, inducted with hyper-CVAD, reduced-intensity conditioning	Tacrolimus, prednisone	Male recipient with matched-related sister	6 years, 7 months	Asymptomatic eczema-like cutaneous lesions, ill-defined brownish. Erythematous plaques, desquamation	Dense epidermal lichenoid infiltrate with atypical lymphocyte with indented, hyperchromatic nuclei, focal epidermotropism, spongiosis	Negative	Gamma	Mixed chimerism	Two-color FISH: Neoplastic cells were XX vs. XY in native cutaneous cells	MF	None
Fahy et al. [5]	Chronic myelogenous leukemia inducted with α-interferon, hydroxycarbamide, conditioned with busulfan, cyclophosphamide and mesna	Cyclosporine, methotrexate, oral steroids	Male recipient with matched-related brother	3 years	Intensely pruritic erythematous, eczematous rash	Dense lymphoplasmacytic infiltrate with focal epidermal tropism by atypical medium-large lymphocytes	Negative	Beta and Gamma	100% donor in peripheral blood, 78% donor in CTCL	Donor's sibling biopsy was initially diagnosed with chronic superficial dermatitis. Later reviews showed mild dermal lymphocytic infiltrate with focal lymphocytis epidermotropism	MF	Involved field radiotherapy, bexarotene, chemotherapy
Loh et al. [6]	Chronic myelogenous leukemia inducted with α-interferon, conditioned with busulfan, cyclophosphamide	Cyclosporine, methotrexate, prednisone	Male recipient with matched-related sister	7 years	Erythematous plaque	“consisten with MF”	Unknown	Gamma	Unknown	At the same time of rash development, donor was diagnosedwith MF. Review of photos prior to transplant noted donor to have a rash.	MF	Clobetasol, narrow band UVB phototherapy, desatinib, bexarotene
Kinsella et al. [2]	Chronic myelogenous leukemia treated with dasatinib, conditioned with fludarabine, melphalan, in vivo T-cell depletion with alemtuzumab	Cyclosporine, prednisone	Female recipient with matched-unrelated male	3 years	Pruritic, lichenoid, erythrodermic rash, accompanied by lymphadenopathy	Atypical T-lymphocytic infiltrate with folliculotropism	Negative	beta	Unknown	Microsatellite and XY-FISH consistent with donor origin	MF	Gemcitabine, ECP, brentuximab

donor derived. T-cell receptor (TCR) gene rearrangement studies were positive for clonal beta and gamma gene rearrangements. In-situ hybridization study for Epstein–Barr virus-encoded small RNAs (EBER) was negative. Positron emission tomography (PET) scan was negative for evidence of hypermetabolic lymphadenopathy or organomegaly. Prior skin biopsy was re-examined with multiple deeper sections and revealed dermal lymphocytic infiltrate composed almost entirely of CD4+ T-cells with CD4:CD8 ratio >10:1 (Fig. 1C, D). These findings met diagnostic criteria of Sezary syndrome. Immunosuppression reduction did not result in decrease of circulating clonal T-cells or improvement of erythroderma. The patient was treated with extracorporeal photopheresis (ECP) for two consecutive days every two weeks with complete resolution of erythroderma and pruritis after four treatments. Periodic monitoring of peripheral blood with flow cytometry identified residual Sezary cells until completion of fifth treatment and subsequently remained cytologically and phenotypically negative. Follow-up TCR gene rearrangements continued to show persistent gamma and beta gene rearrangements suggesting a possibility of minimal residual disease. The patient decided against maintenance therapy with ECP.

3. Discussion

PTLD is a rare but well-recognized complication of alloHSCT. An overwhelming majority (86%) of cases are donor-derived and B-cell origin, frequently associated with EBV (>90%), and manifesting within six months to one year post transplantation [1]. Even more rare, but recognized, is EBV-negative PTLD that are also donor-derived but most often of T and NK cell origin that typically present after one year post-transplant [2–4]. While patients with PTLD of T-cell origin are well-documented post solid organ transplantion, there has only been a handful of reports of T-cell lymphoma following alloHSCT since the early 2000s [5]. Most recently a few cases of CTCL following alloHSCT were described [Table 1]. Santos-Briz et al. reported the first case of post-transplant primary cutaneous T-cell lymphoproliferative disorder after alloHSCT in 2009, in which a male patient with mantle cell lymphoma underwent a matched-related donor alloHSCT and developed asymptomatic eczema-like cutaneous lesions six years after his transplant. Skin biopsy revealed dense superficial lichenoid infiltrate, mainly consisting of CD4+ atypical lymphocytes with clonal TCR gamma rearrangement. EBER was negative. Based on the findings, the patient was diagnose with PTLD consistent with CTCL, mycosis fungoides (MF) type. Although chimerism studies showed mixed donor-recipient DNA, two-color fluorescence in situ hybridization of chromosomes showed that the neoplastic cells had normal female karyotype, 46 XX, in contrast to transplant recipient's cutaneous cells which carried male karyotype, 46, XY [3]. Three other cases of donor-derived PTLD of mycosis fungoides type have been reported since that time. Two cases received matched-related donor and one matched-unrelated donor allograft. Dermatitis, in an otherwise asymptomatic patient, presented from three to eight years following alloHSCT [2,5,6]. In the two matched-related donor cases, the patient's sibling donor also developed rash and was diagnosed with mycosis fungoides at around the time of diagnosis of the recipient; the recipient was found to have 100% donor engraftment [5,6]. In the matched-unrelated donor case, the patient also developed a rash three years after alloHSCT. The initial lichenoid rash with granulomatous features was suggestive of cutaneous sarcoidosis. Patient was treated with hydroxychloroquine, prenisolone and cyclosporine with some improvement but two months later, she developed erythroderma with palpable lymphadenopathy. A repeat skin biopsy was consistent with a diagnosis of folliculotropic mycosis fungoides. Malignant cells revealed CD3+, CD4+, dim CD7 immunophenotype in the skin infiltrate. Similar to present case, EBER was negative, TCR beta gene rearrangement was positive and the malignant clone was confirmed to be of donor origin with a male karyotype [2]. Although underlying malignancy leading to the need for alloHSCT vary from case to case, there are many features that are shared in these cases and in present patient. These include alloHSCT complicated by GVHD requiring immunosuppression, development of rashes, biopsy-confirmed donor-derived malignant cells with negative EBER and positive clonal TCR gene rearrangements. Since allograft donors undergo rigorous testing and patients with history of malignancy are usually excluded from donor participation, it is unlikely that Sezary cells were directly transmitted from the donor. A more plausible explanation is the effect of immunosuppression with development of PTLD by selection and immune evasion of malignant clones. We were not able to obtain medical records of the donor to rule out development of MF/SS. Recent genetic study of 19 patients with PTLD of T cell origin using targeted sequencing and high-resolution copy number analysis suggested that gene and genomic alterations in these diseases are similar to those identified in immunocompetent patients with peripheral T-cell lymphoma [7]. This case of SS and prior reports of MF emphasize the need for thorough evaluation, including repeat skin biopsies of any persistent dermatitis and the importance of continued monitoring even years after transplantation, and the general recognition of MF/SS as rare a late complication of alloHSCT.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lrr.2018.04.006.

References

[1] N.S. Majhail, Secondary cancers following allogeneic haematopoietic cell transplantation in adults, Br. J. Haematol. 154 (2011) 301–310.
[2] Kinsella F., Kashipaz M., Scarisbrick J., et al. Donor-derived mycosis fungoides following reduced intensity haematopoietic stell cell transplantation from a matched unrelated donor. BMJ Case Rep. 2017 Jan 10;2017.pii:bcr2016216331. doi: 10.1136/bcr-2016-216331. PubMed PMID: 28073814; PubMed Central PMCID: PMC5256493.
[3] A. Santos-Briz, A. Romo, P. Antuez, et al., Primary cutaneous T-cell lymphoproliferative disorder of donor origin after allogeneic haematopoietic stem-cell transplantation, Clin. Exp. Dermatol. 34 (2009) e778–e781.
[4] H. Gill, A.H.W. Ip, R. Leung, et al., Indolent T-cell large granular lymphocyte leukaemia after haematopoeitic SCT: a clinicopathologic and molecular analysis, Bone Marrow Transplant 47 (2012) 952–956.
[5] C.M.R. Fahy, A. Fortune, F. Quinn, et al., Development of mycosis fungoides after bone marrow transplantation for chronic myeloid leukemia: transmission from an allogeneic donor, Br. J. Dermatol. 170 (2014) 462–467.
[6] J. Loh, D. Cassarino, W. Grody, et al., A case of mycosis fungoides transmitted from donor to recipient, and review of literature of T-cell malignancies after transplantation, Clin. Lymphoma, Myeloma, Leukemia 14 (2014) e137–e140.
[7] E. Margolskee, V. Jobanputra, P. Jain, et al., Genetic landscape of T- and NK-cell post-transplant lymphoprolerative disorders, Oncotarget 25 (2016) 37636–37648.