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BRIEF ARTICLES

Syngeneic Donor Hematopoietic Stem Cell Transplantation Is Associated with High Rates of Engraftment Syndrome

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Engraftment syndrome (ES), typically characterized by noninfectious fever, rash, and/or noncardiogenic pulmonary edema, is a complication of autologous and allogeneic hematopoietic stem cell transplantation (HSCT). There are no data on ES after syngeneic HSCT. We retrospectively analyzed syngeneic HSCT outcomes and determined ES incidence, risk factors, and prognostic impact. Thirty-two adult patients with a median age of 46 years (range: 22-60) underwent syngeneic HSCT at our institution between July 1986 and April 2009, primarily for hematologic malignancies (65% lymphoid-including 15% plasma cell; 31% myeloid). The median duration of follow-up was 6.1 years (range: 3.7 months to 18.1 years). Five-year progression-free and overall survival (PFS, OS) was 52% and 67%, respectively. Five-year overall cumulative incidence of relapse and nonrelapse mortality (NRM) was 37.6% and 10.2%, respectively; with increased relapse incidence of 76.3% in myeloid disease ($P = .002$). Fifteen patients (47%) met diagnostic criteria for ES, 10 (67%) of whom received systemic steroids. Five-year PFS was 47% in patients with ES versus 56% in those without ($P = .37$). Five-year OS was 63% with ES versus 71% without ($P = .80$). Five-year cumulative incidence of NRM was 21% with ES versus 0% without ($P = .06$). Five-year cumulative incidence of relapse was 32% with ES and 44% without ($P = .68$). Older age ($P = .05$) and possibly total body irradiation–based conditioning ($P = .09$) were risk factors for developing ES. In multivariable Cox models only diagnosis (myeloid disease) impaired OS and PFS. In summary, we document a high incidence of ES after syngeneic HSCT. The trend of increased NRM after ES requires reevaluation in a larger syngeneic HSCT cohort.

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KEY WORDS: Syngeneic, Transplantation, Engraftment syndrome, Capillary leak syndrome

INTRODUCTION

Engraftment syndrome (ES) is a febrile syndrome occurring during neutrophil recovery following hematopoietic stem cell transplantation (HSCT). It is characterized clinically by noninfectious fever in conjunction with clinical findings such as skin rash, hypoxia, and pulmonary infiltrates, fluid retention and weight gain, organ dysfunction, diarrhea, or encephalopathy in the peri-engraftment period [1-3]. Although described over 15 years ago, ES remains a relatively poorly understood complication of HSCT [1]. Its pathogenesis is thought to involve the release of pro-inflammatory cytokines, systemic endothelial damage, as well as products of neutrophil degranulation and oxidative metabolism [2,4]. ES incidence ranges between 7% and 59% in various reports, in part owing to different diagnostic criteria [1,5]. The diagnostic criteria for ES include those proposed by Spitzer and those by Maiolino et al. [2,3]. The Spitzer criteria are considered more stringent [6,7].

ES is an important diagnosis to make for patients experiencing febrile syndromes during the peri-engraftment period, because it responds dramatically to steroids when administered in a timely fashion and at adequate dose. However, if treatment is delayed or inadequate, ES may progress to irreversible multiorgan

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failure [2,6]. ES has been documented in both allogeneic adult donor and umbilical cord blood donor transplantation, but is best described after autologous HSCT. There are no reports on ES in the context of syngeneic HSCT. However, cases of "syngeneic graft-versus-host disease" (GVHD) have been described (summarized by Latif et al. [8]) that may represent overlap with ES.

We undertook a retrospective study of syngeneic HSCT outcomes, with a focus on ES incidence, risk factors, and its survival impact on adult patients treated at the Dana-Farber Cancer Institute.

PATIENTS AND METHODS

Patients

Between July 1986 and April 2009, 32 myeloablative syngeneic donor transplants were performed in adult patients aged ≤60 years at the Dana-Farber Cancer Institute. All had provided informed consent at the time of transplant, including consent for data analysis.

Two authors (J.K., M.B.) reviewed the inpatient medical records of all syngeneic transplants included in the study. All patients received high-dose conditioning chemotherapy utilizing standard regimens. These included: cyclophosphamide plus total-body irradiation (TBI) (18 patients); busulfan plus cyclophosphamide (5 patients); cyclophosphamide, carmustine plus etoposide (5 patients); melphalan alone (3 patients); cyclophosphamide alone (1 patient). No GVHD prophylaxis, T cell depletion, or preemptive or prophylactic donor lymphocyte infusions were given. HSCT supportive care, including use of growth factors, was as per institutional standard at the time.

Syngeneic donor typing methodologies varied over the time period of this report. In brief, through the mid-1990s, HLA Class I typing was performed by serologic methods only. Starting in 1996, confirmatory HLA Class I typing was done by SSP molecular techniques. HLA Class II typing was also by serology until the early 1990s, when it was replaced by molecular polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) and SSP techniques. Currently, syngeneic twin status is determined by STR genotyping using the ABI Profile Plus Kit Human Identity markers. Concordance at all 9 STR loci plus the amelogenin locus indicates that the probability of being identical twins is >99.9%.

Donor syngeneic hematopoietic stem cells were collected from bone marrow (16 patients) or granulocyte-colony stimulating factor (G-CSF) mobilized peripheral blood (15 patients). One patient received both marrow and peripheral blood stem cells. Neutrophil engraftment was assessed by the days to absolute neutrophil count (ANC) ≥500/μL × 2 days. Comorbidity was determined per the HCT-CI score [9]. ES diagnosis was as per Spitzer, and was based on major and minor criteria [2]. Major criteria comprised fever ≥38.3°C with no infectious etiology; erythodermatous rash involving >25% of body surface area; and noncardiogenic pulmonary edema, with hypoxia and diffuse pulmonary infiltrates. Minor criteria comprised hepatic dysfunction with total bilirubin ≥2 mg/dL or doubling of serum transaminase levels; doubling of serum creatinine; weight gain ≥2.5% over baseline; or transient unexplained encephalopathy. To document ES, 3 major criteria or 2 major and 1 minor criteria are required within 96 hours of neutrophil engraftment. The Spitzer criteria were modified to broaden the time period around neutrophil recovery, as is favored by Dispenzieri et al. [6] and Carreras et al., to engraftment ±7 days [7].

Statistical Analysis

Descriptive statistics were used to summarize patient characteristics. The Wilcoxon rank sum test, chi-square test, or Fisher exact test was used for 2 sample comparisons. All tests were 2-sided. Cumulative incidence curves for relapse and nonrelapse mortality (NRM) were constructed reflecting time to relapse and time to nonrelapse death as competing risks. The difference between cumulative incidence curves in the presence of a competing risk was tested using the Gray method [10]. Time to relapse and time to nonrelapse death were measured from the date of stem cell infusion. Patients who were alive without relapse were censored at the time last seen alive. Overall survival (OS) and progression-free survival (PFS) were calculated using the Kaplan-Meier method. OS was defined as the time from stem cell infusion to death from any cause. PFS was defined as the time from stem cell infusion to relapse, disease progression, or death from any cause. The log-rank test was used for the comparisons of Kaplan-Meier curves. Prognostic factors for OS and PFS were examined in Cox proportional hazards models [11].

RESULTS

Patient, Donor, and Transplant Characteristics

Clinical characteristics of the 32 patients in this study are shown in Table 1. The median patient age was 46 years (range: 22-60). Median follow-up time among survivors was 6.1 years (range: 3.7 months to 18.1 years) post-HSCT. There were 15 male and 17 female patients. The principal diagnoses were heterogeneous, as indicated in Table 1. Twelve percent had low-risk disease (ie, acute leukemia in first complete remission [CR1], myelodysplastic syndrome [MDS] with refractory anemia [RA] or refractory anemia and ring sideroblasts [RARS], chronic myeloid leukemia [CML] in first chronic phase [CP1], lymphoma in CR1). The median

Table 1. Characteristics of Patients Undergoing Syngeneic HSCT with and without Engraftment Syndrome (ES)

	N	No %	N	ES %	ES *P*-Value
Total	17	100	15	100	
Age					
<50	15	88	8	53	.05
≥50	2	12	7	47	
Median (range)	44	(22-55)	48	(25-60)	.12
Gender (male)	7	41	8	53	.72
Diagnosis					
ALL	—	—	1	7	
AML	2	12	1	7	
Anemia/red cell disorder	—	—	1	7	1
CML	2	12	—	—	
MDS	2	12		3	20
Hodgkin Disease		—	—	2	13
MM/plasma cell disorder	4	24		1	7
NHL	7	41		6	40
Diagnosis (subcategorized)					—
Lymphoid	11	65	10	67	
Myeloid	6	35	4	27	
Other	—	—	1	7	
Cell source					.85
Bone Marrow	9	53	7	47	
Peripheral blood stem cells	7	41	8	53	
Both	1	6	—	—	
HCT-CI Comorbidity Score					
Low: 0	9	53	4	27	
Medium: 1-2	2	12	8	53	
High: ≥3	6	35	3	20	
Median (range)	0	(0, 7)	1	(0, 4)	
Steroid therapy					<.0001
No	17	100	5	33	
Yes	—	—	10	67	
Year of transplant					1.00
<2002	10	59	8	53	
≥2002	7	41	7	47	
Disease risk status					.60
High	14	82	14	93	
Low*	3	18	1	7	
Conditioning					.09
TBI	7	41	11	73	
non-TBI	10	59	4	27	
Median time to engraftment (range)	11.5	(5-29)	12	(9-22)	

ALL indicates acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; ES, engraftment syndrome; TBI, total-body irradiation; HSCT, hematopoietic stem cell transplantation.
*AML/ALL in first complete remission (CR1), CML in chronic phase (CP1), MDS with retinoic acid (RA) or retinoic acid receptors (RARS), lymphoma in CR1.

stem cell dose was 5.1 (range: 0.5-21.9) × 10^6 $CD34^+$ cells/kg.

There were 15 patients with ES (median age: 48; range: 25-60) and 17 patients without ES (median age: 44; range: 22-55). Of the patients with ES, 10 (67%) were prospectively diagnosed during HSCT, and received a short course of systemic steroids with prompt resolution of symptoms in all but 1 case. The median follow-up time among survivors with and without ES was 6.1 years (range: 6.3 months to 18 years) and 5.2 years (range: 3.7 months to 10.8 years), respectively. ES and non-ES groups did not differ significantly with regard to covariates of sex donor stem cell source (peripheral blood stem cell [PBSC] versus bone marrow), diagnosis (myeloid versus lymphoid); disease risk at transplant (low versus high risk), time to neutrophil engraftment, HCT-CI comorbidity score, and year of transplant (<2002 versus ≥2002); but did differ with regard to patient age (<50 versus ≥50 years) (P = .05), and possibly with regard to conditioning regiment (TBI versus non-TBI) (P= .09) (Table 1).

Survival Outcomes

For the syngeneic HSCT cohort, 5-year PFS was 52% (95% confidence interval, 32-69); and OS was 67% (95% CI, 45-81). The 5-year overall cumulative incidence of relapse and NRM was 37.6% and 10.2%, respectively (Figure 1A). When stratified by diagnosis, relapse risk, but not NRM, was increased in patients with myeloid disorders versus those with lymphoid (including plasma cell) disorders, at 76.3% versus 17% (P = .002) and 10% versus 10.4% (P = .95), respectively (Figure 1B).

Comparing ES patients versus those without ES, 5-year PFS was 47% (95% CI, 20-71) versus 56% (95% CI, 26-78; P = .37) (Figure 1C). Five-year OS

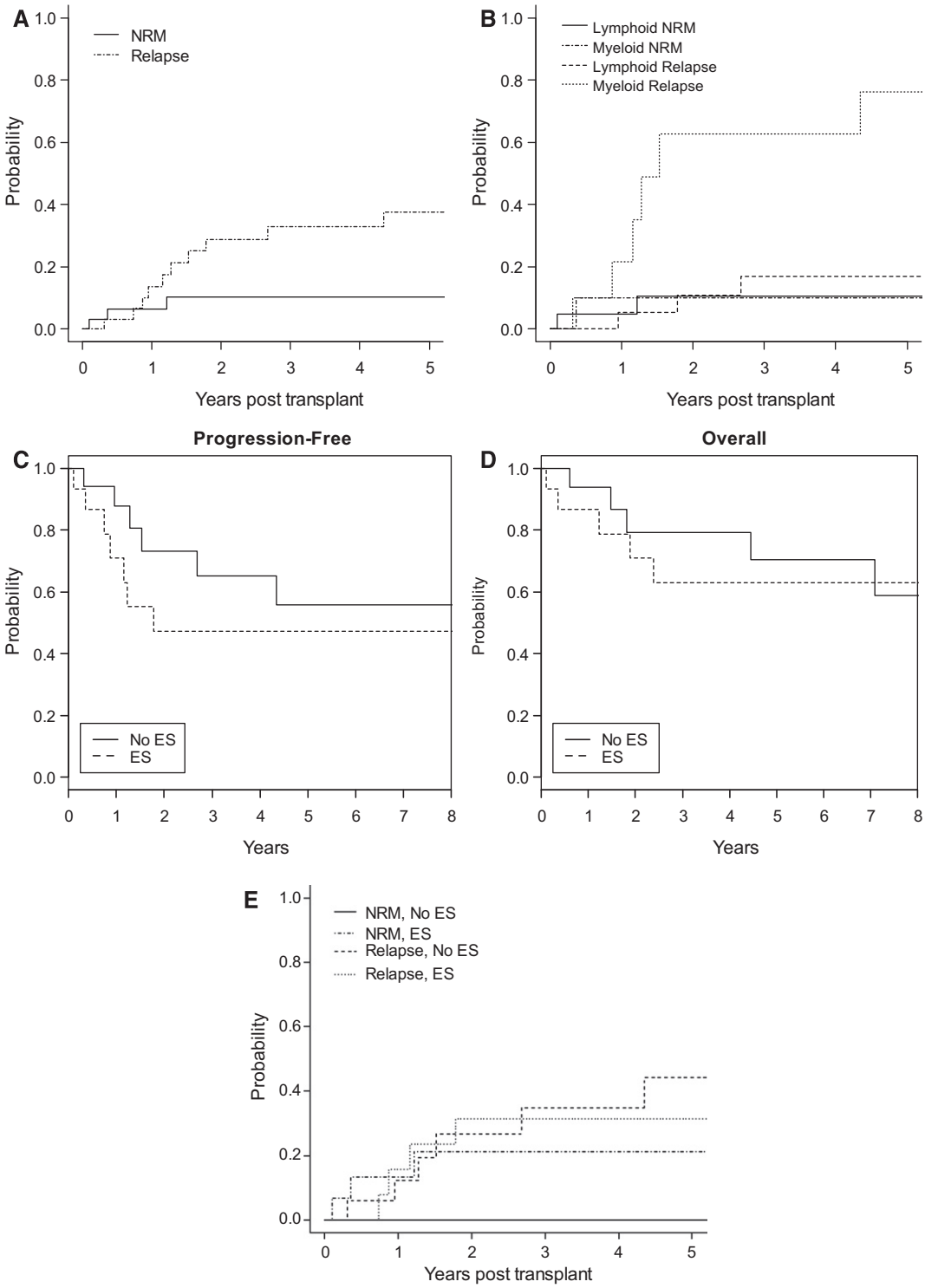

Figure 1. (A) Cumulative incidence of relapse and NRM as competing risks—overall. (B) Cumulative incidence of relapse and NRM as competing risks—by diagnosis (n = 31). (C) Progression-free survival—by ES cohort. (D) Overall survival—by ES cohort. (E) Cumulative incidence of relapse and NRM as competing risks—by ES cohort.

in ES patients versus those without ES was 63% (95% CI, 32-83) versus 71% (95% CI, 39-88; $P = .80$), respectively (Figure 1D). Five-year cumulative incidence of NRM was 21% for patients with ES versus 0% without ES ($P = .06$). Five-year cumulative incidence of relapse was 32% for patients with ES versus 44% without ES ($P = .68$) (Figure 1E). Similar 5-year PFS and OS outcomes were noted when the ES cohort was restricted to the 10 patients treated with steroids ($P = .14$; $P = .52$, respectively).

Table 2. Multivariable Cox Models—Adjusted Model (Age, Sex and Year of Transplant Are Adjusted for Each Model*)

Model		OS			PFS		
Variable (+ Age + Gender + Transplant)	n	HR	95% CI	P	HR	95% CI	P
Engraftment syndrome versus none	32	1.16	0.33-4.03	.81	1.77	0.58-5.46	.32
Disease risk status, high versus low	32	1.07	0.12-9.42	.95	1.66	0.24-11.72	.61
Time to engraftment (continuous)	32	0.98	0.87-1.11	.74	0.97	0.86-1.10	.62
Diagnosis, myeloid versus lymphoid†	31	8.47	1.73-41.58	.009	4.83	1.33-17.53	.017
HCT-CI, high versus low/medium	32	0.54	0.11-2.72	.45	0.58	0.14-2.50	.47
Conditioning, TBI versus no TBI	32	1.21	0.28-5.19	.80	0.77	0.20-2.97	.70

OS indicates overall survival; PFS, progerssion-free survival; HR, hazard ratio; CI, confidence interval; TBI, total-body irridiation.
Note: Wald test *P* value for the coefficient.
*For each model, age, sex and year of transplant were nonsignificant.
†One patient with diagnosis of "other" was not included in this model.

Multivariable Models

We evaluated the impact of ES in a multivariable Cox model of survival outcomes (PFS, OS) (Table 2). Because of the limited sample size, patient age (continuous), sex and year of transplant (<2002 versus ≥2002) were included in every model and comorbidity score (HCT-CI: high versus moderate/low), diagnosis (myeloid versus lymphoid), disease-risk (high versus low) time to engraftment (continuous), conditioning regimen (TBI versus non-TBI), or ES (present versus absent) was added separately. Survival outcomes were significantly impaired in patients with myeloid disorders, with PFS and OS hazard ratios of 4.83 (95% CI, 1.33-17.53, $P = .017$) and 8.47 (95% CI, 1.73-41.58, $P = .009$), respectively. No other covariate, including ES, was associated with OS and PFS endpoints.

DISCUSSION

ES, a complication of HSCT, classically comprises a maculopapular skin rash and noninfectious fever, with or without fluid retention and weight gain, hypoxia with noncardiogenic pulmonary edema, among others. ES is best described after autologous HSCT, but also reported in the allogeneic UCB and adult donor context. However, ES incidence, risk factors, and impact on survival outcomes needs to be more fully characterized.

Our understanding of the pathogenesis of ES remains limited, even in the context of autologous HSCT. Various risk factors for the development of ES in patients with hematologic disease undergoing autologous HSCT have been described, including female sex [5], prior chemotherapy [12], increased number of infused hematopoietic cells [5,13], peripheral blood as a source of stem cells [1,5], accelerated neutrophil reconstitution [5,14], and use of G-CSF and granulocyte macrophage-colony stimulating factor (GM-CSF) [15]. Most ES risk factors have not been reproducible across studies. With regard to outcome, most studies have not reported impaired survival in patients with ES, although there are exceptions [16].

There is no information on ES in the context of syngeneic HSCT. Although rare, syngeneic transplantation represents an opportunity to better understand ES because there are fewer clinical variables in syngeneic HSCT. For instance, unlike autologous HSCT, variables of tumor contamination, prior cancer chemotherapy, and impact of chemotherapy-based stem cell mobilization are nonrelevant for syngeneic donor cells. Also, unlike allogeneic HSCT, variables of donor sex and age, HLA-match, ABO-match, GVHD prophylaxis, and incidence are not relevant in syngeneic HSCT.

This is the first report on ES in the context of syngeneic HSCT. It comprises a sizeable cohort of 32 transplants undertaken in a single institution with extended follow-up over the past 23 years. Previously, individual case reports have documented "syngeneic GVHD" over the years, summarized by Latif et al. [8], who identified a total 19 cases in the medical literature from 1979 to 2003. "Syngneic GVHD" has some overlapping features with ES, for instance, maculopapular skin rash was described in all cases, typically during the peri-engraftment period (7-21 days posttransplant); and for the ~50% who received it, therapy typically comprised steroids (±cyclosporine). However, the overlap with ES remains uncertain, given other discordant features in "syngeneic GVHD," such as lack of reported fever; and the fact that some patients had recurrent symptoms at up to 303 days posttransplant, despite extended therapy.

In our syngeneic HSCT cohort, ES is frequent, involving 47% of patients. Of these, two-thirds were prospectively diagnosed and received steroid therapy, as is appropriate. However, one-third of ES cases were not diagnosed in a timely fashion, highlighting the clinical relevance of considering ES in the differential diagnosis of febrile syndromes after syngeneic HSCT. The steroid-treated patients experienced prompt resolution of ES symptoms (with 1 exception, who died of respiratory failure), and experienced no GVHD flare after rapid taper of steroids, confirming the DNA-identical nature of the transplant. Three ES patients had NRM. As previously mentioned, 1

patient died on day +41 post-HSCT, of progressive acute respiratory distress syndrome (ARDS) in the context of ES, despite treatment with steroids. The second ES patient (also prospectively treated with steroids) died of parainfluenza pneumonitis and ARDS at ~4 months post-HSCT, and the third ES patient (not prospectively treated with steroids), died of congestive heart failure (CHF) with dilated cardiomyopathy, ascites, and portal hypertension of unclear etiology at ~15 months post-HSCT.

Our study has limitations. As a retrospective single-institution analysis it is subject to bias, for instance, in patient referral, selection for HSCT, and possibly in the determination of complex clinical events from the medical record. Additionally, given the long time period involved in accruing patients receiving this rare therapeutic modality, secular changes in clinical practice involving HSCT selection, methodology, and supportive care impact this analysis. For instance, variables such as $CD34^+$ stem cell dose and growth factor use were not systematically documented during the earlier time periods of this analysis (ie, prior to the mid–late 1990s). Furthermore, although this 32-patient cohort is large for a rare therapeutic modality like syngeneic HSCT, it does limit our ability to undertake detailed statistical analyses and confirm clinically meaningful associations.

Nonetheless, some notable findings have emerged. In addition to documenting a 47% incidence of ES after syngeneic HSCT, we identified patient age ≥50 years as a risk factor for developing ES ($P = .05$), with a possible role for TBI-based conditioning ($P = .09$). Of clinical concern is the finding that patients with ES had 5-year cumulative incidence of NRM of 21% versus 0% for those without ES ($P = .06$). Although of borderline statistical significance, it raises concerns that ES may have clinically relevant longer-term impact. Notably, steroid therapy, despite inducing prompt symptom resolution, did not reduce NRM risk. In our cohort, 2 of 10 ES patients receiving steroid therapy and 1 of 5 ES patients not receiving steroid therapy experienced NRM, an identical 20% incidence. We therefore suggest that the impact of ES on NRM should be evaluated in a larger multi-institutional analysis.

We also note a strikingly higher overall relapse incidence (but not NRM) and impaired survival in patients with myeloid disorders undergoing syngeneic HSCT. This is in line with published meta-analyses indicating overall lack of benefit of autologous transplant as a consolidative modality in myeloid malignancies [17-19]. Considering that tumor contamination is not an issue with syngeneic grafts, the high relapse incidence speaks to the importance of the allogeneic graft-versus-leukemia response in myeloid malignancies, likely dependent on mismatch at minor HLA loci.

In summary, this is the first report on ES in patients undergoing syngeneic HSCT. We identify ES as a frequent event after syngeneic HSCT, indicating the need for a high index of suspicion for this diagnosis. Older patient age (and possibly TBI-based conditioning) was a risk factor for ES. The possibility of increased NRM incidence after syngeneic ES needs further evaluation.

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AUTHORSHIP STATEMENT

J.K. and R.J.S. did the research design; J.K., E.P.A., C.C., P.A., J.H.A., R.J.S., V.T.H., and C.J.W. did patient care; J.K., M.B., J.A., H.T.K. did data collection; J.A. and H.T.K. did statistical analysis; J.K. did manuscript preparation; all authors did manuscript editing and review.

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APPENDIX

Table 1. Clinical Features of ES Patients during Syngeneic HSCT

No.	Age	Sex	Disease	Year	Rash*	Fever†	Pulmonary‡	Hepatic§	Renal¶	CNS⊥	GI**	Steroids	Notes
1	55	F	NHL	1999	YES	YES	NO	YES	NO	NO	YES	YES	Rash, fever, transaminitis, diarrhea during engraftment.
2	59	F	AA	1998	YES	YES	YES	NO	NO	NO	NO	YES	Rash, fever, pulmonary infiltrates. Steroids for diffuse alveolar hemorrhage.
3	34	M	NHL	1988	YES	YES	YES	YES	YES	NO	NO	YES	Fevers, rash, pulmonary infiltrates. Died on D+41 of ARDS
4	47	F	MM	2006	YES	YES	YES	YES	NO	NO	YES	YES	Rash, fever, hypoxia, hepatic dysfunction, diarrhea during engraftment.
5	25	M	HD	1990	YES	YES	NO	YES	NO	NO	YES	NO	Fever, rash, diarrhea, hepatic dysfunction. Rash initially thought antibiotic-related but persisted.
6	30	F	ALL	2003	YES	YES	NO	NO	NO	NO	YES	YES	Rash, fever, diarrhea. Received course of steroids for ES vs. GVHD.
7	43	M	NHL	1995	YES	YES	YES	NO	NO	YES	YES	YES	Fever, diffuse rash, pulmonary infiltrates, diarrhea and intermittent confusion.
8	39	M	NHL	1986	YES	YES	NO	YES	YES	NO	YES	NO	Fever, diarrhea, hepatic/renal dysfunction, generalized rash during engraftment.
9	48	F	MDS	1996	YES	YES	NO	NO	YES	NO	YES	YES	Fever, rash, diarrhea. Rash initially considered folliculitis, then 'GVHD'.
10	59	F	MDS	2003	YES	YES	YES	NO	NO	NO	NO	YES	Diffuse erythematous rash considered 'GVHD' vs. ES.
11	60	M	NHL	1994	YES	YES	NO	NO	YES	NO	NO	NO	Persistent diffuse rash and fever, and transient renal dysfunction during engraftment.
12	57	M	MDS	2006	YES	YES	YES	YES	NO	NO	YES	YES	Fever, rash, profuse diarrhea, hepatic dysfunction. Initially thought drug reaction, then ES.
13	54	M	NHL	2006	YES	YES	NO	NO	YES	NO	YES	YES	Fever, diffuse rash, diarrhea and transient renal dysfunction.
14	53	F	AML	2009	YES	YES	NO	YES	NO	NO	YES	NO	Persistent fevers, diarrhea and new onset rash during engraftment.
15	37	M	HD	2009	YES	YES	NO	YES	NO	NO	YES	NO	Diffuse rash, fevers, hyperbilirubinemia and profuse diarrhea peri-engraftment.

N.B.: 1) Weight gain ≥2.5% baseline was not reliably quantified.
2) Diarrhea is considered an ES criterion by Maiolino et al. [3], and is included for completeness.
*Rash: erythrodermatous rash ≥25% of body surface area, not attributable to a medication.
**GI: noninfectious diarrhea of at least 2 liquid bowel movements/day without identifiable infection.
†Fever: temperature ≥100.9 F with no identifiable infectious etiology.
‡Pulmonary: noncardiogenic pulmonary edema; with diffuse pulmonary infiltrates, hypoxia.
§Hepatic: total bilirubin ≥2 mg/dL or hepatic transaminases ≥2× normal.
¶Renal: serum creatinine ≥2× baseline.
⊥CNS: transient encephalopathy unexplainable by other causes.