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Case report

Engraftment syndrome: a common cause for rash and fever following autologous hematopoietic stem cell transplantation for multiple sclerosis

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Summary:

Autologous hematopoietic stem cell transplantation (HSCT) is currently being evaluated as a therapy for patients with progressive multiple sclerosis (MS) at risk of debilitating neurological impairment. While preliminary results from a few studies have been reported, little is known about toxicities or outcome of HSCT for MS. We report a relatively frequent triad of non-infectious fever, rash and fatigue or lassitude that may also be associated with pruritis, pulmonary symptoms, and eosinophilia and frequently occurs around engraftment. This syndrome occurred in 26% of our series of patients (5/19) undergoing HSCT for multiple sclerosis. The engraftment syndrome is usually self-limited but may require intervention with systemic corticosteroids.
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MS is generally considered to be an immune-mediated demyelinating disease, and is commonly treated with immune modulating therapies including interferon-beta (Avenox, Betaseron) and copolymer 1 or glatiramar acetate (Copaxone). When these agents fail to produce an adequate response, corticosteroids, mitoxantrone, cyclophosphamide, azathioprine, methotrexate or cladribine may be added or substituted.[1–9] Hematopoietic stem cell transplantation (HSCT) is now being offered to patients with progressive disease because: (1) current non-specific immune suppressive therapies are not curative and only slow progression;[1–9] (2) there is insufficient knowledge on the etiology and pathogenesis of MS and specific antigenic targets, particularly when applied across race and HLA phenotypes to design highly specific immune therapies; (3) there is a desperate need for more effective therapy perceived by both physician and patients due to the increased suicide rate in some series of MS.[10]

The concept of HSCT for MS has been proposed[11] and partially supported by results of HSCT in experimental autoimmune encephalomyelitis (EAE), an animal autoimmune demyelinating CNS disease.[12–20] The first reported use of HSCT for MS was by Fassas *et al*[21] in Thessoliniki, Greece, using a carmustine, etoposide, cytarabine, melphalan (BEAM) conditioning regimen. The first North American HSCT for MS utilized a cyclophosphamide and total body irradiation regimen (Cy/TBI).[22] BEAM has subsequently become the standard MS transplant regimen in Europe, while Cy/TBI-based regimens are the most common regimen utilized for HSCT of MS in North America.[23–38]

We report on a uniquely frequent complication of HSCT using Cy/TBI for MS seen in approximately one quarter of our subjects. This syndrome of fever, rash and fatigue with generalized non-focal neurologic weakness is usually self-limited and occurs around the time of engraftment and generally resolves within 2–3 weeks irrespective of treatment. Clinical and histologic features of the rash may mimic acute cutaneous graft-versus-host disease (GVHD).

Method

A retrospective review of HSCT performed for MS at Northwestern University Medical Center was performed to identify all patients with an engraftment syndrome defined as unexplained erythematous rash, non-infectious fever (temperature $>38.1°C$), and generalized non-focal and transiently increased fatigue or weakness within 60 days of HSCT.

Hematopoietic stem cell collection

Hematopoietic stem cells (HSC) in the first two subjects were collected from iliac crest bone marrow. However, due to the low yield, supplemental collection from peripheral blood was used to obtain the minimum of 2.0×10^6 $CD34^+$ stem cells/kg body weight. Collections of HSC from subsequent subjects were obtained solely from peripheral blood. Initially, HSC were mobilized by administering gra-

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nulocyte colony-stimulating factor (G-CSF) 10 μg/kg/day for 5 to 6 days. Leukapheresis was performed on day 4 or 5 and, if necessary to generate sufficient HSC, the next day using a continuous flow blood cell separator (either Fenwall CS3000; Baxter, Deerfield, IL, USA or Cobe Spectra; Cobe Lakewood, CO, USA). Due to flare of disease activity in subject 5, while receiving G-CSF alone for mobilization, subsequent HSC were collected by infusion of cyclophosphamide (2.0 g/m^2) followed by daily G-CSF (5 μg/kg/day) beginning 72 h after cyclophosphamide infusion. Leukapheresis was initiated when the white blood cell count rebounded to more than 1000 $\times$ 10^6/l (usually 10 days after cyclophosphamide administration). The peripheral blood was enriched for CD34$^+$ HSC by passage through either a CEPRATE SC stem cell concentrator (CellPro, Bothell, WA, USA) or Isolex stem cell separator (Nexell, Irving, CA, USA). The enriched stem cell product was frozen with a controlled rate freezer (Gordinier Electronics, Roseville, MI, USA) and stored in the vapor phase of liquid nitrogen.

Conditioning regimen

Immune ablation was achieved over 6 days by administration of cyclophosphamide 60 mg/kg once daily i.v. on days 1 and 2 (total dose 120 mg/kg) followed by total body irradiation (TBI) in doses of 150 cGy twice daily for 4 consecutive days yielding a total dosage of 1200 cGy to the midplane at the level of the umbilicus. Radiation was administered in the AP/PA position with 50% of dose attenuation to the lungs, 20% to the right lobe of the liver, and 30% to the kidneys. Radiation was delivered using 10 mv photons at a dose rate of approximately 10 cGy/min. *In vivo* dosimetry was performed on each subject to confirm the accuracy of radiation doses delivered to multiple body points. One gram of methylprednisolone was administered i.v. on each of the 4 days of TBI. HSC were infused on the day following TBI (day 0).

Supportive care

Subjects were treated in a HEPA filtered medical floor or general clinical research center. They were fed a low microbial diet. Prophylactic antimicrobials included ciprofloxacin, fluconazole and valacyclovir starting upon admission. Ciprofloxacin was switched to piperacillin/tazobactam when absolute neutrophil count (ANC) was less than 500 $\times$ 10^6/l and was stopped upon WBC engraftment, defined as ANC $\geqslant$500 $\times$ 10^6/l. Fluconazole and valacyclovir were continued for 6 months following HSC transplantation. Either trimethoprim/sulfamethoxazole or a pentamidine nebulizer was started after engraftment and continued for 6 months. Irradiated/leukoreduced packed red blood cells and single donor platelets were administered to all subjects to maintain a Hb above 8 g/dl and a platelet count above 30 $\times$ 10^9/l. G-CSF was administered at 5 μg/kg from the day of HSC infusion until the ANC reached $\geqslant$1000 $\times$ 10^6/l.

Results

Nineteen patients with multiple sclerosis have undergone autologous CD34-enriched HSCT at Northwestern University with no mortality. Of these, 26% (5/19) have developed a transient engraftment syndrome. This syndrome is characterized by fever, fatigue and increased weakness along with variable combinations of rash, eosinophilia, and pulmonary symptoms. The rash clinically and histologically is similar to GVHD. It usually involves the upper chest and back and lower neck, but may extend to legs and forearms. The rash is erythematous, maculopapular and follicular in appearance (Figure 1). Skin biopsy of involved areas demonstrates finding consistent with acute GVHD (Figure 2).

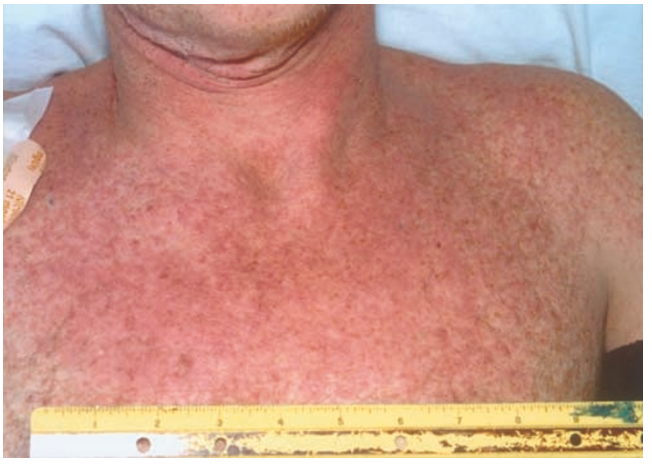

Figure 1 Maculopapular rash resembling acute graft-versus-host disease.

Fever may be low-grade (38.1°C) or higher (39.4°C) and investigations including fungal and bacterial blood cultures, CT scans of chest and sinuses, CMV antigenenia assay, and central line removal and tip culture failed to reveal an infectious etiology. Fever resolved spontaneously, independent of anti-microbial intervention. Pulmonary symptoms occurred in two patients and included rhinorrhea, persistent dry cough and transient oxygen desaturation that spontaneously resolved coincidental with resolution of rash and fever. Eosinophilia ($>$500 $\times$ 10^6/l) occurred in three

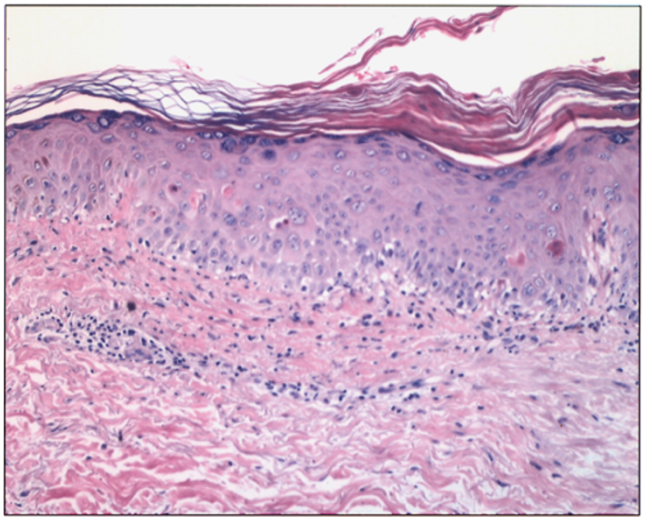

Figure 2 Skin biopsy demonstrated dyskeratotic keratinocytes, basal layer vacuolization and infiltration of mononuclear cells in parafollicular bulge consistent with acute GVDH.

Table 1 Occurrence of engraftment syndrome in patients with multiple sclerosis undergoing HSCT

Patient	*Age*	*Sex*	*CMV serology status*	*CD34⁺ × 10⁶/kg*	*CD3⁺ × 10⁵/kg*	*WBC engraft day*	*Platelet engraft day*	*Fatigue*	*Fever °C (onset date)[f]*	*Eosinophil × 10⁶/l*	*Pulmonary symptoms*	*Rash (day of onset)*	*Treatment*
1	44	F	+	2.05	5.38	12	12	yes	38.9 (d23)	5610	no	yes (d23)	MP 1.0 g i.v × 3 days
2	34	F	–	2.40	13.6	12	12	yes	no	0	no	yes (d11)	none
3	35	F	–	2.03	10.4	12	12	no	no	272	no	no	—
4	39	M	–	3.14	2.28	13	11	no	no	0	no	no	—
5	44	F	+	2.05	5.15	11	29	no	no	300	no	no	—
6	21	F	–	2.62	0.93	19	19	no	no	0	no	no	—
7	34	F	–	8.68	1.19	10	17	no	no	200	no	no	—
8	48	M	–	3.70	2.15	12	21	no	no	0	no	no	—
9	52	M	–	3.06	0.04	10	10	yes	39.4 (d22)	1000	no	yes (d22)	none
10	44	F	–	4.66	2.02	12	13	no	no	0	no	no	—
11	24	M	–	10.00	0.13	10	11	no	no	0	no	no	—
12	40	M	+	7.93	0.26	12	11	no	no	100	no	no	—
13	40	M	–	4.13	0.09	11	11	yes	38.6 (d7)	300	no	yes (d7)	none
14	47	F	+	5.77	0.13	10	10	no	no	400	no	no	—
15	52	M	+	5.30	0.16	11	10	yes	38.5 (d6)	100	yes – rhinorrhea, dry cough, hypoxemia	yes (d6)	MP 1g i.v. × 5 days then p.o. prednisone taper
16	29	M	+	5.38	0.13	10	10	no	no	100	no	no	–
17	50	F	–	9.50	0.10	11	11	no	no	100	no	no	–
18	28	M	–	7.57	0.11	16	20	yes	38.3 (d27)	800	Yes (dry cough)	yes (d53)	prednisone p.o.
19	45	M	+	4.42	0.05	10	10	yes	no	0	no	yes (d16)	none

i.v. = intravenous; MP = methylprednisolone; p.o. = oral.

patients, resolving spontaneously in one and after corticosteroids in two others. In all cases, fever was associated with increased generalized and transient fatigue and weakness, with greater limitation on activities of daily living compared to pre-admission. Duration of fever and rash varied from 5 to 14 days. Although due to sample size formal statistical analysis was omitted, occurrence of engraftment syndrome did not have an obvious correlation with $CD34^+$ cell dose, $CD3^+$ cell dose, age, sex or CMV status (Table 1).

Discussion

We report a post-transplant complication of autologous HSCT for multiple sclerosis consisting of fever, rash and lassitude or fatigue occurring in five of 19 (26%) patients. This engraftment syndrome is usually transient and may not require treatment. Criteria for treating with corticosteroids for this unanticipated syndrome were based upon attending clinical discretion (Table 1). In MS, fever, independent of its etiology, often causes transient worsening of neurological symptoms known as a pseudo-exacerbation, due to slowing of nerve conduction velocity and increased conduction blockade.[29,30] Not surprisingly, engraftment syndrome is accompanied by fatigue and lassitude. While fatigue is a subjective symptom, compared to a normal person, temperature-dependent fatigue is common in patients with MS.[29,30] The rash appears similar to acute GVHD, and in those who underwent skin biopsy, is histologically indistinguishable from acute GVHD.

An engraftment syndrome has been previously reported to occur following autologous HSCT for solid tumors and hematological malignancies, and is characterized by non-infectious fever, rash and noncardiogenic pulmonary edema.[31–35] In autologous HSCT for solid tumors, engraftment syndrome has been associated with capillary leak and pulmonary infiltrates.[31,35] The absence of pulmonary edema or infiltrates in our patients may be due to radiation lung blocks used to diminish the risk of pulmonary toxicity. Etiology of engraftment syndrome is unknown. Prompt resolution of fever with systemic corticosteroids suggests an early post-transplant immunologic dysregulation.

Spitzer[36] recently suggested criteria for engraftment syndrome. Although our patients do not meet those criteria completely, and onset may be 12 days after WBC engraftment, the presence of rash independent of drugs, non-infectious fever, and histological evidence of acute skin GVHD would reasonably confirm the diagnosis of engraftment syndrome. For the purpose of this report, we do not draw a distinction between engraftment syndrome and autologous GVHD.

In European studies, the engraftment syndrome has not been reported for MS patients treated with BEAM conditioning, suggesting a toxicity more common to Cy/TBI conditioning in MS. In another American study, by Nash *et al*,[24] one patient had sustained fever of unknown origin with an increased disability score that could potentially have been a similar phenomenon. At Northwestern University, the engraftment syndrome has not occurred in any of 12 systemic lupus erythematosus, four rheumatoid arthritis or two Crohn's disease patients who underwent autologous HSCT. Only one of these patients received a TBI-containing regimen, and all non-MS autoimmune patients who underwent HSCT were on corticosteroids during the transplant. A short course of post-transplant corticosteroids may be indicated to help prevent the engraftment syndrome, which in MS is associated with increased weakness, fatigue and decline in performance status.

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