はじめに

移植片対宿主病（graft-versus-host disease: GVHD）は，同種造血幹細胞移植後の重篤な合併症の一つである。ステロイド薬の全身投与はGVHDに対する標準的な治療法であるが，感染症の増加など副作用が問題となる。

ジプロピオン酸ベクロメタゾン（beclomethasone dipropionate: BDP）は，本邦において気管支喘息・アレルギー性鼻炎に対する吸入剤として一般に使用されている。BDPは肺や腸管から吸収後[1]，エステラーゼにより急速に分解され主要活性代謝物である17-モノプロピオン酸ベクロメタゾン（beclomethasone-17-monopropionate: 17BMP）に代謝され，17BMPはステロイド活性をもたないベクロメタゾン（beclomethasone: BOH）へ代謝される[2]。BDPは初回通過効果により大部分が代謝されることから，全身的な作用は少ないことが報告[3-5]されている。こうした体内動態の特性から，経口BDPは消炎活性が局所に限定される[6]ステロイド薬として期待され，腸管GVHDに対する有効性が報告[7-12]されてきた。BDPは局所作用が大部分であり全身的な副作用は少ないと考えられているが，腸管GVHD患者を対象に経口BDPの血中濃度を測定した報告はない。

今回われわれは，腸管GVHD患者における経口BDPの吸収の程度を確認するため，BDPおよびその代謝物の血中濃度について検討したので報告する。

Ⅰ．対象と方法

1．対　象

対象は2006年10月～2007年1月まで同種造血幹細胞移植後，腸管GVHD（急性，慢性を含む）を発症し，院内製剤経口ベクロメタゾンを投与した患者である。血中濃度の測定については，文書により十分な説明に従い同意が得られた患者を対象とした。

本研究における経口BDPの投与および血中濃度測定は虎の門病院倫理審査委員会において承認を得ている。

2．院内製剤経口ベクロメタゾンと規格

院内製剤経口ベクロメタゾンはMP Biomedical社のジプロピオン酸ベクロメタゾンの原末を使用し，院内製剤した。院内製剤経口ベクロメタゾンはカプセル剤とシロップ剤の二つの剤型とし，それぞれ名称をBDPカプセルとBDP内服液とした。BDPカプセルは小腸で溶解後，小腸および大腸に活性薬物が供給され下部消化管で作用することを期待して腸溶カプセルとした。BDP内服液は，上部消化管に作用することを期待してシロップ剤とした。院内製剤経口ベクロメタゾンの規格に関しては，BDPカプセル1カプセル中1 mgのBDP，BDP内服液30 mL中1 mgのBDPを含有するように院内製剤した。

3．BDPカプセルとBDP内服液の投与方法と血中濃度測定時間

投与方法は，全対象症例においてBDPカプセルは1回1カプセルを1日4回（6，11，16，21時），BDP内服液は1回30 mLを1日4回（カプセル服用の15分後），経口投与した。

血中濃度測定は，BDP投与開始後3日目以降でBDPカプセル服用約4時間後（BDP内服液服用後3時間45分）を目安とした。

4．BDP，17BMP，BOHの血中濃度測定方法

BDP，17BMP，BOHの血中濃度測定は，Applied Biosystems/MDS SCIEX社のAPI 3200™ LC-MS-MS system（LC-MS/MS）で行った。

高速液体クロマトグラフィ（high-performance liquid chromatography: HPLC）のカラムはSymmetry Shield™ RP8 5 μm 2.1×150 mm Column（Waters Corps.）を用い，LC-MS/MSで測定を行った。BDP，17BMP，BOHの検出範囲は250～5,000 pg/mLとし，検出限界は250 pg/mLとした。

5．17BMPの血中濃度と腸管GVHDのstageの関連

腸管GVHDの程度と経口BDPの吸収を検討した。腸管GVHDの重症度分類は造血細胞移植ガイドラインに従って行った。腸管GVHDの評価は血中濃度測定日に行った。

Ⅱ．結　果

1．患者背景と採血時間

対象患者は5例であった。患者背景をTable 1に示した。患者の年齢は20歳台から60歳台であり，原疾患は急性骨髄性白血病3例，急性リンパ性白血病1例，慢性骨髄性白血病1例であった。移植細胞源は，臍帯血2例，骨髄1例，同種末梢血2例であった。

採血時間は，症例2～5ではBDPカプセル服用4.5時間後であったが，症例1ではBDPカプセル服用1.5時間後であった。

2．BDP，17BMP，BOHの血中濃度

対象患者の血中濃度測定結果をTable 2に示した。BDPカプセル服用1.5時間後に測定した症例1は，17BMPの血中濃度が2,439±161 pg/mLまで上昇した。BDPカプセル服用4.5時間後に測定した4例全例で，17BMPは618～1,749 pg/mLの範囲の血中濃度で検出された。BDPは全例，BOHは2例で検出感度以下であった。

Table 1 Patients' background

Patient No.	Age	Sex	Diagnosis	Stem cell source	Onset of gut GVHD	Start day of BDP	Stage of gut GVHD at BDP starting	Day of blood sampling	Stage of gut GVHD at blood sampling
1	65	female	ALL	CB	day 136	day 141	3	day 159	1
2	32	male	AML	BM	day 93	day 94	2	day 120	3
3	62	female	AML	PBSC	day 120	day 122	3	day 156	3
4	68	male	AML	CB	day 31	day 29	2	day 70	2
5	28	male	CML	PBSC	day 46	day 46	2	day 52	1

ALL: acute lymphoblastic leukemia, AML: acute myelogenous leukemia, CML: chronic myelogenous leukemia, CB: cord blood, BM: bone marrow, PBSC: peripheral blood stem cell

Table 2 Blood concentration of BDP, 17BMP, and BOH

Patient No.	Interval between blood sampling and BDP administration (hour)	BDP	17BMP	BOH
		mean±SD (pg/mL)		
1	1.5	nd	2,439±161	751±63
2	4.5	nd	1,166±184	358±32
3	4.5	nd	1,749±208	339±22
4	4.5	nd	618±19	nd
5	4.5	nd	696±74	nd

nd: not detectable

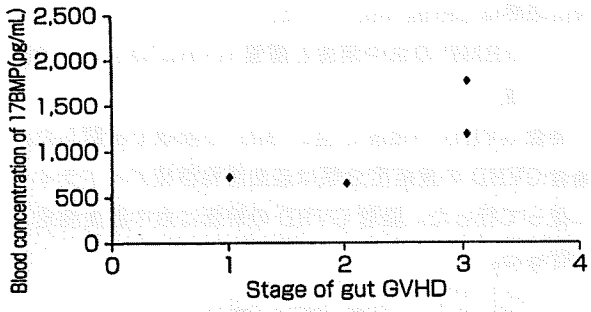

Fig. 1 Blood concentration of 17BMP and stage of gut GVHD at blood sampling

3. 17BMPの血中濃度と腸管GVHDのstageの関連

腸管GVHDの重症度と経口BDPの吸収を検討するため，17BMPの血中濃度と腸管GVHDのstageの関連をFig. 1に示した。症例1は服用1.5時間後に採血したため解析対象から除外した。解析症例4例のうち，腸管GVHDに伴う症状は全例下痢でありstage 1は1名，stage 2は1名で，17BMPの血中濃度はそれぞれ696，618 pg/mLであった。stage 3は2名で，17BMPの血中濃度はそれぞれ1,166，1,749 pg/mLであった。腸管GVHDのstageと17BMPの血中濃度の関連を検討したところ，腸管GVHDのstageが高い症例では17BMPの血中濃度が高値である傾向が認められた。

Ⅲ. 考 察

全対象患者5例でBDPの主要活性代謝物である17BMPが血中で検出された。1995年のMcDonaldらの研究[7]では，経口BDPを投与した腸管GVHD患者20例中11例（55%）に副腎抑制を認めたことより経口BDPは吸収され，全身的な副作用が発症し得ることが示唆されている。2001年に報告[2]された健常人を対象とした研究において，BDPの経口投与によりわずかながら全身的な吸収を有することが報告されている。今回，われわれの研究結果は，McDonaldらが副腎抑制により間接的にBDPの吸収を示唆した報告と健常人でBDPが吸収された報告を支持する結果となった。

健常人でのBDP 1,000 μgの単回吸入投与の報告[13]によると，17BMPの血中濃度は2,103 pg/mLであった。また，BDPの吸入剤であるキュバール®において，BDP 400 μgを軽度から中程度の気管支喘息患者に単回吸入投与した際の17BMPの血中濃度は1,419 pg/mL[14]であった。今回の研究では1回2 mg（カプセル1 mg，内服液1 mg）を1日4回投与したが，5例中4例において17BMPの血中濃度は618～1,749 pg/mLであった。これはBDP 1回400～1,000 μgを単回吸入投与した時（1,419～2,103 pg/mL）と同程度あるいはそれ以下の血中濃度であることが確認された。吸入剤投与時のBDP 1日投与量が1,500 μgまでの場合，副腎皮質系抑制の有意な危険性はないとの報告[15]があることより，吸入剤と

同程度の血中濃度であれば副腎皮質系抑制の危険性は低いと考えられる。1例は，17BMPの血中濃度は2,439±161 pg/mLで吸入剤投与時以上の血中濃度の上昇がみられた。

健常人を対象とした研究[2]で経口BDP服用後の17BMPの最高血中濃度到達時間が4時間であったことより，本研究は血中濃度測定時期をBDPカプセル服用約4時間後としたが，実際の測定時間は，症例1はBDPカプセル服用1.5時間後，症例2～5は4.5時間後であった。BDPカプセル服用1.5時間後に測定した症例1の17BMPの血中濃度は2,439 pg/mLと5症例のうち最高値を示した。症例1は，BDP開始時の腸管GVHDのstageが3であり高度の腸管粘膜障害を呈していた。腸管輸送（運動）能が保持されていて，粘膜障害も高度でないstage 1および2の患者では，健常者と同程度のTmaxである可能性があるものの，stage 3以上の腸管GVHD患者では，最高血中濃度到達時間は健常人と異なる可能性を有すると考えられる。

腸管GVHDのstage 1とstage 2の症例における17BMPの血中濃度はそれぞれ696，618 pg/mLであり，健常人にBDP 4 mgを単回経口投与し服用4時間後の最高血中濃度（703 pg/mL）[2]と比較して同程度の血中濃度であった。腸管GVHDのstage 3の症例2名の17BMPの血中濃度は1,166，1,749 pg/mLであり，健常人の血中濃度と比較しそれぞれ1.7，2.5倍と高値を示したことから，GVHDのstageが高い患者では健常人よりも血中濃度が上昇する可能性が示唆された。また，腸管GVHDのstageが高い症例で17BMPの血中濃度が高値である傾向が認められた原因として腸管GVHDの重症度，つまり腸管粘膜障害の程度が高まるにつれて経口BDPの吸収が亢進し，血中濃度が上昇した可能性がある。特に重度の腸管GVHDが発症している症例は，経口BDPによる全身的な副作用の発現の可能性を考慮すべきである。

文　献

1) 相良博典：吸入ステロイド薬の吸収特性と安全性．アレルギー科　19(5)：421-428，2005.
2) Daley-Yates PT, Price AC, Sisson JR, *et al*: Beclomethasone dipropionate: absolute bioavailability, pharmacokinetics and metabolism following intravenous, oral, intranasal and inhaled administration in man. *Br J Clin Pharmacol*　51: 400-409, 2001.
3) Brattsand R: Airways-lung selectivity of inhaled steroids. アレルギーの領域　5(10): 1410-1415, 1998.
4) Phillipps GH: Structure-activity relationships of topically active steroids: the selection of fluticasone propionate. *Respir Med*　84(*suppl* A): 19-23, 1990.
5) Hubner M, Hochhaus G, Derendorf H, *et al*: Comparative pharmacology, bioavailability, pharmacokinetics, and pharmacodynamics of inhaled glucocorticosteroids. *Immunol Allergy Clin North Am*　25(3): 469-488, 2005.
6) 大石孝義，出口隆志，丸茂博大：Beclomethasone 17，21-dipropionateの代謝．応用薬理　22(5)：717-727，1981.
7) Baehr PH, Levine DS, Bouvier ME, *et al*: Oral beclomethasone dipropionate for treatment of human intestinal graft-versus-host disease. *Transplantation*　60(11): 1231-1238, 1995.
8) McDonald GB, Bouvier M, Hockenbery DM, *et al*: Oral beclomethasone dipropionate for treatment of intestinal graft-versus-host disease: a randomized, controlled trial. *Gastroenterology*　115: 28-35, 1998.
9) Castilla C, Perez-Simon FA, Sanchez-Guijo FM, *et al*: Oral beclomethasone dipropionate for the treatment of gastrointestinal acute graft-versus-host disease (GVHD). *Biol Blood Marrow Transplant*　12: 936-941, 2006.
10) Hockenbery DV, Cruickshank S, Rodell TC, *et al*: A randomized placebo-controlled trial of oral beclomethasone dipropionate as a prednisone-sparing therapy for gastrointestinal graft-versus-host disease. *Blood*　109(10): 4557-4563, 2007.
11) 山本久史，内田直之，内田ゆみ子・他：同種造血幹細胞移植後の消化管GVHDに対する経口ベクロメタゾン療法．臨血　47(9)：239，2006.
12) Miura Y, Narimatsu H, Kami M, *et al*: Oral beclomethasone dipropionate as an initial treatment of gastrointestinal acute graft-versus-host disease after reduced-intensity cord blood transplantation. *Bone Marrow Transplant*　38: 577-579, 2006.
13) Lipworth BJ and Jackson CM: Pharmacokinetics of chlorofluorocarbon and hydrofluoroalkane metered-dose inhaler formulations of beclomethasone dipropionate. *Br J Clin Pharmacol*　48: 866-868, 1999.
14) キュバールエアゾール®医薬品インタビューフォーム，第10版，大日本住友製薬株式会社，大阪，2006，p16.
15) Ip M, Lam K, Ng M, *et al*: Decreased bone mineral density in premenopausal asthma patients receiving long-term inhaled steroids. *Chest*　105(6): 1722-1727, 1994.

Possible graft-versus-host disease involving the central nervous system soon after cord blood transplantation

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The concept that central nervous system (CNS) could be a target of graft-versus-host disease (GVHD) is controversial. There are a few case reports which support the possibility of CNS-GVHD [1,2]. Here, we describe a patient who developed unique CNS symptoms soon after cord blood transplantation with reduced-intensity conditioning (RI-CBT). On Day 7 post-transplant, a high fever, slight skin eruption, moderate diarrhea, and liver damage suddenly developed. Three days later, her white blood cell (WBC) count rapidly increased to 1,700 μl^{-1} and consisted mostly of mature lymphocytes. Generalized convulsions developed on the same day. An analysis of the cerebrospinal fluid (CSF) revealed elevated proteins and pleocytosis comprising mostly mature lymphocytes. The lymphocytes found in the peripheral blood (PB) and CSF were phenotypically polyclonal T-cells that were donor derived. Extensive investigations did not detect any microorganisms or other causes for the T-cell proliferation and CNS symptoms. Considering the coexistence of CNS and systemic GVHD-like symptoms, proliferation of donor-derived polyclonal T-cells in the CSF and PB, and no microorganisms or other factors detected, CNS GVHD seems to be the most likely explanation for her clinical course.

Cord blood (CB) has been increasingly applied as a viable source of stem cells for allogeneic hematopoietic stem cell transplantation (allo-SCT) [3,4]. The incidence and severity of GVHD following cord blood transplantation (CBT) are lower than those after allo-SCT using bone marrow or peripheral blood stem cells from either matched siblings or unrelated donors [5–7]. On the other hand, unique immune-mediated complications, such as pre-engraftment immune reaction (PIR) and hemophagocytic syndrome (HPS), have been observed early after RI-CBT [8,9]. Thus, the spectrum of immune-mediated reactions after RI-CBT has not yet been fully clarified.

CNS complications have been described following allo-SCT [10]. Infections, drug toxicity, and metabolic and cerebrovascular disorders are the major causes, and there have been rare cases of apparent immune-mediated reaction to CNS [1,2].

Here, we present an interesting case of a patient who developed unique CNS symptoms soon after RI-CBT. A 40-year-old woman with follicular lymphoma that was refractory to chemotherapy was admitted to our hospital in September 2006. Her clinical stage was IV B at diagnosis in 2002. Six cycles of rituximab (R)-CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) resulted in complete remission, and rituximab therapy was maintained for 1 year. A relapse occurred in 2005 and was treated with R-ACES (high-dose Ara C, carboplatin, etoposide, and steroids), R-ICE (ifosfamide, carboplatin, etoposide), cladribine, and R-COP (cyclophosphamide, vincristine, and prednisone), which resulted in a partial response at each cycle. However, the disease gradually progressed thereafter, with the development of systemic lymphadenopathy, pleural effusion, and ascites. Since no suitable related or unrelated donors from the Japan Marrow Donor Program were available, unrelated CB was considered as an alternative graft, and she was referred to our hospital. The patient and graft were sex-mismatched and phenotypically two and genotypically three-loci mismatches in HLA-A, HLA-B, and DRB1 loci. The types of the HLA-A, HLA-B, and DRB1 loci were *A01* (*0101*)/A31 (3101), B35 (3501)/*B48* (*4801*), and DRB1*04

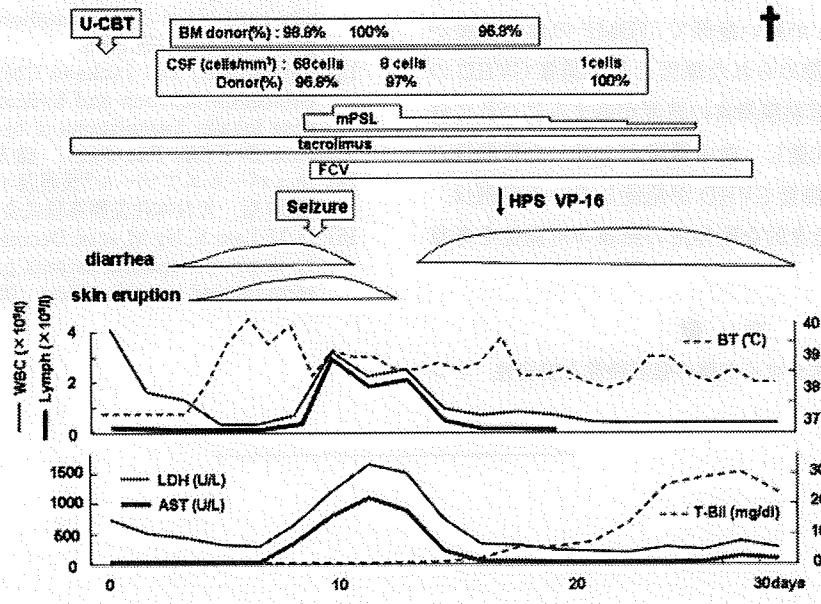

Figure 1. Clinical course of the patient. Abbreviations: U-CBT, unrelated cord blood transplantation; BM, bone marrow; CSF, cerebrospinal fluid; mPSL, methylprednisolone; FCV, foscarnet; HPS, hemophagocytic syndrome; VP-16, etoposide; WBC, white blood cell; BT, body temperature; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; T-bil, total bilirubin.

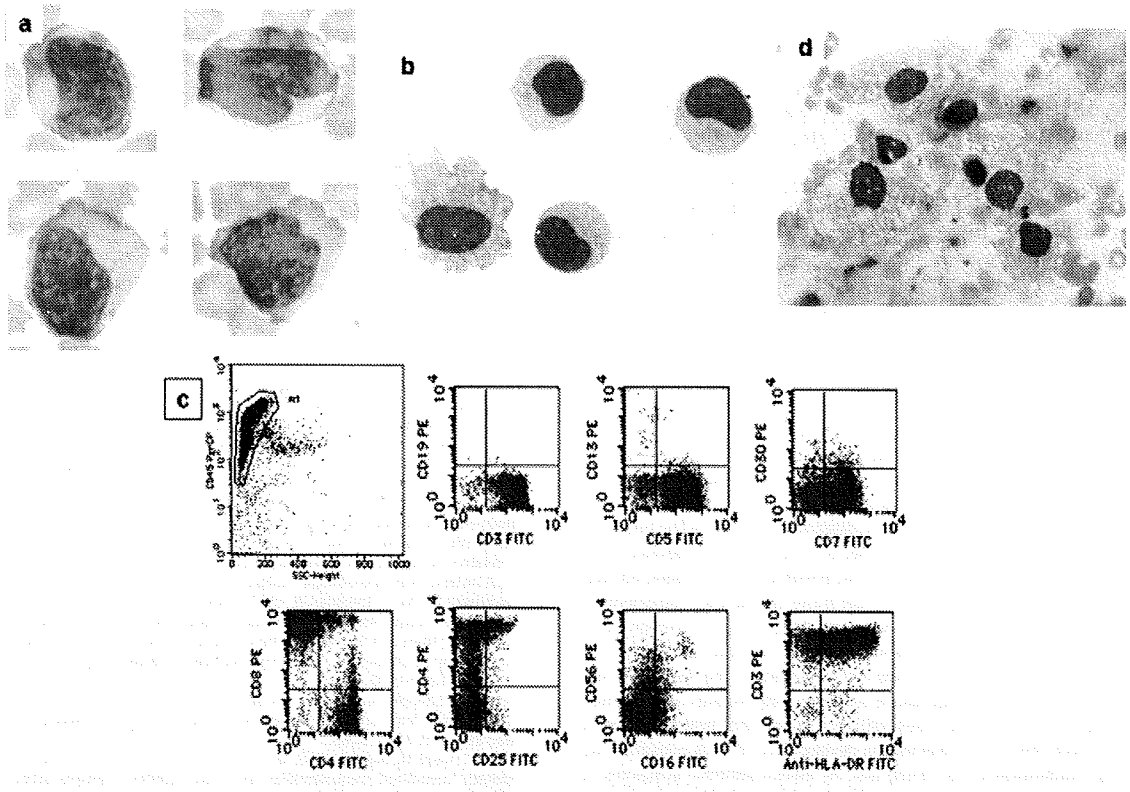

Figure 2. Activated lymphocytes in peripheral blood (a) and in cerebrospinal fluid (b) on Day 10 post-transplant. Flow cytometry of peripheral blood on Day 10 post-transplant (c). Activated macrophages in bone marrow on Day 17 post-transplant (d). May-Giemsa staining ×1000 (a, b) ×400 (c). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

(*0404*)/DRB1*09 (0901), respectively, in the recipient, and *A26* (*2601*)/A31 (3101), B35 (3501)/*B51* (*5101*), and DRB1*04 (*0401*)/DRB1*09 (0901), respectively, in the donor. The graft contained 2.4 × 10^7/kg total nucleated cells and 0.92 × 10^5/kg CD34$^+$ cells. The pretransplant conditioning regimen consisted of fludarabine (25 mg/m^2/day) for 5 days, melphalan (40 mg/m^2/day) for 2 days, and 4 Gy of total body irradiation. Tacrolimus alone was administered as GVHD prophylaxis. Granulocyte colony-stimulating factor was started from Day 1. Pretransplant viral serology was positive for HSV, HVZ, CMV, and EBV, and negative for HIV and HTLV-1. She received 600 mg/day of oral acyclovir, 400 mg/day of oral tosufloxacin, 200 mg/day of oral itraconazole, and trimethoprim-sulfamethoxazole (160 mg/day of the trimethoprim component) as for antimicrobial prophylaxis. Figure 1 shows her entire clinical course following RI-CBT. On Day 7 post-transplant, a high fever, slight skin eruption, and moderate diarrhea developed with a slightly increased WBC count (from 10 μl^{-1} on Day 6 to 30 μl^{-1} on Day 7). Her WBC count rapidly increased on Day 10 to 1,700 μl^{-1} and comprised 90% lymphocytes (Fig. 2a). Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels increased to 715 and 359 IU/l, respectively, and serum lactate dehydrogenase (LDH) levels increased to 1,101 IU/l. The patient suddenly lost consciousness along with generalized convulsions on the same day and required mechanical ventilation. Cerebrospinal fluid (CSF) analysis revealed an extremely elevated protein level of 675 mg/dl (normal range: 15–40 mg/dl) and pleocytosis (68 cells/μl), consisting mainly of lymphocytes (98%) (Fig. 2b). Magnetic resonance imaging scans of the brain revealed no specific abnormalities typically seen in cerebrovascular disorders, tacrolimus encephalopathy, thrombotic microangiopathy, or other CNS complications, and schistocytes were undetectable in the PB. Flow cytometry revealed that the excessive lymphocytes in both PB and CSF comprised polyclonal mature T-lymphocytes expressing CD3, CD4, CD5, CD8, and HLA-DR. The expression of CD4 and CD8 was variable, in which CD4$^-$CD8$^+$, CD4$^+$CD8$^-$, and CD4$^+$CD8$^+$ cells accounted for 65, 25, and 9%, respectively, of the cells in PB, and 38, 56, and 6%, respectively, of those in the CSF (Fig. 2c). Y chromosome-based fluorescence in situ hybridization analysis showed that most of these cells were derived from the donor (98.8% in PB and 96.8% in CSF). Furthermore, 98% of BM cells obtained on Day 10 were also donor derived. Routine cultures of PB and CSF for bacteria and fungi were negative. Analyses by real-time polymerase chain reactions were negative for HSV-1, HHV-6, VZV, CMV, and EBV in PB and CSF, and, for HSV-2, HSV-7, HSV-8, JCV, BKV, ADV, Parvovirus B19, HBV, and HCV in PB. Southern blotting of cells from the PB showed that the genes for both T-cell receptor Cβ1 and Jδ1 were in germ-line configuration, and EBV genome clonality was undetectable. Methylprednisolone (500 mg/day) was administered for 3 days, and acyclovir was switched to foscarnet, considering the possibility of acute GVHD and viral infection insensitive to acyclovir. After the initiation of these therapies, the numbers of lymphocytes in PB and CSF gradually decreased, and her clinical symptoms and laboratory data improved, so methylprednisolone was carefully tapered. However, high fever, diarrhea, and CNS symptoms recurred around Day 17, and then pancytopenia and cholestatic liver damage rapidly progressed. On Day 17, BM aspiration revealed an increase of activated macrophages (35%) with massive hemophagocytosis (Fig. 2d). The chimeric status of the BM cells revealed sustained donor cell dominance (96.8%), indicating that the hematopoietic cells and macrophages in the BM were both donor derived. Despite the administration of etoposide (50 mg/m^2) to control the hemophagocytosis, pancytopenia and cholestatic liver damage progressed and the patient died of bacterial sepsis 32 days after transplantation. An autopsy was not performed.

Polyclonal T-cell proliferation is the principal mechanism of the antigen-specific immune response that generally occurs upon infection and/or inflammation. GVHD is also primarily a T-cell-mediated event, and the subsequent expansion of donor T-cell clones-recognizing antigens causes tissue damage either directly through T-cells encountering recipient MHC-bearing cells in target tissues or indirectly through cytokine production [11].

We previously reported higher incidence of immune-mediated complications, such as PIR, characterized by high-grade fever, skin eruption, diarrhea, jaundice, and body weight gain developing before engraftment, and HPS early after RI-CBT [8,9]. Despite the known immunological naïvety of CB cells, the exceptionally high incidence of PIR and HPS suggests that the properties of CB cells are unique and distinctly different from adult donor cells.

The most striking features of our patient were the remarkable polyclonal T-cell proliferation both in PB and CSF, followed by sudden generalized convulsions and loss of consciousness. As the coexistent CNS and systemic GVHD-like symptoms, proliferating donor-derived polyclonal T-cells in the CSF and PB, and microorganisms or other factors that might be responsible for these symptoms or T-cell proliferation were undetectable. We therefore postulated that an alloimmune reaction of the CB graft against the CNS caused the CNS symptoms in our patient.

The concept that CNS could be a target of GVHD is controversial. Some case reports support the possibility of CNS-GVHD [1,2]. All of the patients in these reports were diagnosed with CNS-GVHD only when they responded to immunosuppressive therapy and had histologically and immunophenotypically documented perivascular T-cell infiltration without evidence of other CNS diseases with overlapping features. However, uniform diagnostic approaches or criteria have not been established. Most of the reported CNS-GVHD was diagnosed at the time of chronic GVHD development. Powles et al. [12] reported that convulsions, possibly due to cerebral edema, could develop as a manifestation of severe acute GVHD after haploidentical transplantation. This could explain the events in our patient, although information about the CSF, the presence or absence of T-cell proliferation, or detectable infectious organisms was not provided in the literature. We reported that early CNS complications are more frequent after RI-CBT than after transplantation with other stem cell sources and that hypercytokinemia associated with PIR could influence the development of CNS complications [13]. T-cell proliferation in CSF along with the severe systemic symptoms in our patient might have resulted from a type of hypercytokinemia that is unique to RI-CBT.

Moreover, severe HPS developed around 10 days after T-cell proliferation, and the activated macrophages in the BM were donor derived. Although HPS is a rare complication following allo-SCT, some investigators have suggested that a severe alloimmune response could result in HPS after PB transplantation [14,15]. Furthermore, we recently reported that the incidence of HPS following RI-CBT is higher than was previously reported and that HPS is a significant risk factor for engraftment failure [9]. Hypercytokinemia associated with engrafted T-cell proliferation may have played an important role in donor-derived macrophage activation and in the development of HPS in our patient.

In conclusion, we described a patient who developed sudden generalized convulsions and lost consciousness at the same time as polyclonal T-cell proliferation soon after RI-CBT. The findings of extensive investigations indicated that the CNS can be a target of GVHD. Further accumulation of clinical and laboratory data with the awareness of this devastating complication soon after RI-CBT is warranted to precisely understand the underlying basic mechanisms and to develop optimal intervention strategies.

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References

1. Kamble RT, Chang CC, Sanchez S, et al. Central nervous system graft-versus-host disease: Report of two cases and literature review. Bone Marrow Transplant 2007;39:49–52.
2. Padovan CS, Bise K, Hahn J, et al. Angiitis of the central nervous system after allogeneic bone marrow transplantation? Stroke 1999;30:1651–1656.
3. Rocha V, Gluckman E. Clinical use of umbilical cord blood hematopoietic stem cells. Biol Blood Marrow Transplant 2006;12:34–41.
4. Brunstein CG, Setubal DC, Wagner JE. Expanding the role of umbilical cord blood transplantation. Br J Haematol 2007;137:20–35.
5. Takahashi S, Iseki T, Ooi J, et al. Single-institute comparative analysis of unrelated bone marrow transplantation and cord blood transplantation for adult patients with hematologic malignancies. Blood 2004;104:3813–3820.
6. Takahashi S, Ooi J, Tomonari A, et al. Comparative single-institute analysis of cord blood transplantation from unrelated donors with bone marrow or peripheral blood stem-cell transplants from related donors in adult patients with hematologic malignancies after myeloablative conditioning regimen. Blood 2007;109:1322–1330.
7. Rocha V, Labopin M, Sanz G, et al. Transplants of umbilical-cord blood or bone marrow from unrelated donors in adults with acute leukemia. N Engl J Med 2004;351:2276–2285.
8. Kishi Y, Kami M, Miyakoshi S, et al. Early immune reaction after reduced-intensity cord-blood transplantation for adult patients. Transplantation 2005; 80:34–40.
9. Takagi S, Masuoka K, Yamamoto H, et al. Risk factors for the development of hemophagocytic syndrome following reduced-intensity umbilical cord blood transplantation. EBMT Annual Meeting 2007. O368 S43 [abstract].
10. Siegal D, Keller A, Xu W, et al. Central nervous system complications after allogeneic hematopoietic stem cell transplantation: Incidence, manifestations, and clinical significance. Biol Blood Marrow Transplant 2007;13:1369–1379.
11. Morris ES, Hill GR. Advances in the understanding of acute graft-versus-host disease. Br J Haematol 2007;137:3–19.
12. Powles R, Pedrazzini A, Crofts M, et al. Mismatched family bone marrow transplantation. Semin Hematol 1984;21:182–187.
13. Kishi Y, Miyakoshi S, Kami M, et al. Early central nervous system complications after reduced-intensity stem cell transplantation. Biol Blood Marrow Transplant 2004;10:561–568.
14. Abe Y, Choi I, Hara K, et al. Hemophagocytic syndrome: A rare complication of allogeneic nonmyeloablative hematopoietic stem cell transplantation. Bone marrow Transplant 2002;29:799–801.
15. Kishi Y, Kami M, Murashige N, et al. Hyperacute GVHD and emergence of peripheral CD3+CD56+ T-cells and activated natural killer cells are useful markers for early diagnosis of post-transplant hemophagocytic syndrome. Bone Marrow Transplant 2005;35:415–417.

Treatment with hydroxyurea in a patient compound heterozygote for a high oxygen affinity hemoglobin and β-thalassemia minor

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Compound heterozygotes for β-thalassemia and high oxygen affinity hemoglobin (Hb) have been documented, but experience in the management of such rare cases is minimal. Although hydroxyurea (HU) has never been used in a heterozygote with high oxygen affinity Hb and β-thalassemia, we hypothesized that it would decrease erythrocytosis through a lowered production of abnormal cells and increase of P_{50} by induction of fetal hemoglobin (HbF). We present the case of a patient with compound high oxygen affinity Hb mutation with β-thalassemia. PCR analysis revealed combined Hb Regina and IVS1-110 G/A mutations. Treatment with HU caused a decrease in Ht (61.1% to 38.6%) and erythrocyte volume (74.87 mL/kg to 40.65 mL/kg), as well as an increase in P_{50} (6 mmHg to 10 mmHg) and HbF level (3.6% to