CASE REPORT

Central Nervous System-related Graft-versus-host Disease after Allogeneic Hematopoietic Stem Cell Transplantation

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Abstract:
Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the only curative therapy for refractory hematological malignancies. However, there are many treatment-related complications, including organ disorders, graft-versus-host disease (GVHD), and infectious diseases. Furthermore, there are many unclear points regarding central nervous system (CNS) complications, and the prognosis in patients with CNS complications is extremely poor. We herein report a 49-year-old woman who developed CNS-GVHD after a second transplantation for therapy-related myelodysplastic syndrome. CNS-GVHD in this case was refractory to all treatments, including steroids, and progressed. We also present a review of the literature about the symptoms, diagnosis, and treatment of CNS-GVHD.

Key words: allogeneic hematopoietic stem cell transplantation, graft-versus-host disease, central nervous system complications, central nervous system graft-versus-host disease

Introduction

Although an effective anti-tumor effect can be achieved through conditioning regimens and donor cells in allogeneic hematopoietic stem cell transplantation (allo-HSCT), there are many treatment-related complications, including organ disorders, graft-versus-host disease (GVHD), and infectious diseases, the prevention and treatment of which are important to improve the survival rate. Of these, there are many unclear points regarding central nervous system (CNS) complications. Since the prognosis of patients with CNS complications is extremely poor, an accurate diagnosis and early therapeutic intervention when neurological symptoms occur are important. In a report by Sakellari et al. with 758 cases of allo-HSCT, 16.8% were found to have CNS complications, with the most common complication being infection (37.3%) (1). In contrast, among non-infectious causes, the most common cause was the recurrence of the original disease in the CNS (17.4%), microthrombosis (9.4%), and hemorrhaging (5.2%).

The frequency of GVHD has steadily declined due to the recent increase in the use of human leukocyte antigen (HLA) analyses and advanced immunosuppressive drugs. However, it is the main cause of relapse-free death. The skin, digestive tract, and liver are considered the main target organs of GVHD; however, all organs aside are potential targets, and the pathological conditions are varied. Although CNS-GVHD is a cerebrovascular disease or acute/chronic inflammatory demyelinating polyneuropathy, its frequency is rare, its diagnosis is often difficult, and there is no standardized treatment (1).

We herein report the results of the pathological examination of a case of progressive consciousness disorder post-allo-HSCT suspected of being CNS-GVHD based on the clinical course and a review of related published reports.

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The patient was a 49-year-old woman with no relevant family history. She had a history of ovarian cyst and anal cancer treated with fluorouracil, mitomycin C, and 54 Gy of radiation. Pancytopenia was observed from December Year X-2. A bone marrow examination in January Year X-1 revealed two strains of dysplasia and chromosomal abnormalities [complex karyotype: 44, XX, -5, del(7)(q?), -8, add(12)(p11.2), -14, add(17)(p11.2), -18, +mar1, +mar2 (2 cells)/45, idem, -add(17), +18, -21, +mar3, +mar4 (4 cells)]; an increase in the proportion of blast cells in the bone marrow (>5%) was observed, and therapy-related myelodysplastic syndrome [therapy-related myeloid neoplasms, WHO 2016 (Revised International Prognostic Scoring System: very high)] was diagnosed (2).

Seven courses of azacitidine (AZA) therapy resulted in complete hematological remission; an unrelated allogeneic bone marrow transplantation [HLA allele full match (8/8)] was performed in late September, Year X-1. There were a few complications, such as GVHD, and the patient was discharged on day 52 post-transplantation. At discharge, the patient was only on the immunosuppressant tacrolimus (5 mg/day) and had no symptoms of GVHD. However, pancytopenia reappeared in April Year X (7 months after transplantation), and a bone marrow examination in the same month with fluorescence in situ hybridization for the X and Y chromosomes showed the following: recipient, 15.5%; and chromosomal abnormality with complex karyotype 45, X, add(X)(p22.1), -4, der(5;17)(p10;q10), add(7)(q22), -8, add(12)(p11.2), +2mar. Therefore, the patient was diagnosed with MDS recurrence. Despite two courses of AZA therapy, the pancytopenia did not improve, so a second allogeneic hematopoietic stem cell transplantation was scheduled, and the patient was hospitalized in early August, Year X.

The physical findings on admission showed no obvious abnormalities except for palpebral conjunctival pallor. The laboratory findings on admission showed pancytopenia (white blood cell count, 1,700/μL; hemoglobin, 7.3 g/dL; platelet count, 2.1×10⁵/μL), but no blast cells were observed in the peripheral blood. We observed mild renal dysfunction after the previous allo-HSCT (creatinine 1.35 mg/dL, estimated glomerular filtration rate 34 mL/min/m²) and elevation of the biliary enzyme levels (alkaline phosphatase, 1,397 IU/L; γ-glutamyl transpeptidase, 398 IU/L). There were no other notable findings.

Unrelated allogeneic bone marrow transplantation [HLA allele full match (8/8)] was performed in late August, year X, with the following conditioning regimen: fludarabine (30 mg/m²; day -7 to -2), busulfan (3.2 mg/kg; day -5 to day -4), and melphanal (40 mg/m²; day -3 to day -2). For GVHD prevention, tacrolimus + short-term methotrexate [day 1 (15 mg/m²), day 3 (10 mg/m²), and day 6 (10 mg/m²) after transplantation] were administered. Engraftment of neutrophils on day 20, erythrocytes on day 29, and platelets on day 31 was confirmed. The chimerism observed after bone marrow transplantation showed over 90% donor cells on days 45 and 112.

From day 24 post-transplantation, the patient complained of weakness in her limbs; her energy gradually decreased, and her consciousness gradually deteriorated. On day 34, as indicated by the Japan Coma Scale II-20, flaccid paralysis of both upper and lower limbs was observed, and an increase in the deep reflex (tendon reflex/Chaddock reflex) was observed. Magnetic resonance imaging (MRI) on the same day showed a high-frequency signal in the diffusion-weighted image of the posterior aspect of the periventricular white matter, suggesting reversible occipital leukoencephalopathy, and tacrolimus was discontinued (Fig. 1). Despite having started prednisolone (1 mg/kg/day) after tacrolimus was discontinued, acute GVHD grade II (skin, stage 3; gut, stage 1; and liver, stage 0) appeared. Electroencephalography and single-photon emission computed tomography of the brain were performed, but no specific findings were obtained. In the cerebrospinal fluid on day 34, the cell count was less than 1, total protein level was 55 mg/dL, sugar level was 83 mg/dL, lactate dehydrogenase level was 24 U/L, cytology was negative, and various viral tests (herpes simplex virus type 1, herpes simplex virus type 2, varicella-zoster virus, poliovirus, human herpes virus 6, human herpes virus 7, human herpes virus 8, cytomegalovirus, BK virus, JC virus, Epstein-Barr virus, and hepatitis B virus) were negative.

By day 37 post-transplantation, the lesion had expanded to the corpus callosum and pons; it was thus suggested that the condition might have been caused by an inflammatory state, such as that induced by drugs and GVHD. Therefore, we started methylprednisolone pulse treatment (1 g/day for 3 days) on the same day, and immunized globulin (20 g) was administered on day 39. After methylprednisolone pulse treatment (1 g/day for 3 days), GVHD of the skin and gut gradually improved and there was no recurrence of non-CNS-GVHD. Antibiotics, antifungal agents, and proton pump inhibitors were all changed. Cyclosporin, which was started on day 66 for the treatment of CNS-GVHD, was stopped on day 99 because no clinical improvement had been noted on day 83. We observed bilateral interstitial pneumonia and respiratory syncytial virus antigen positivity; treatment with antibiotics failed, and the respiratory status worsened. Subsequently, brainstem dysfunction progressed, and light reflex, vomiting reflex, and spontaneous breathing disappeared. Respiratory failure and heart failure progressed, and a fatal cardiopulmonary arrest occurred on day 131.

A pathological examination revealed a 4-mm hematoma on the posterior surface of the neurohypophysis, severe degeneration of the occipital lobe white matter, and hemorrhaging and degeneration in the brain stem. A histological examination showed severe degeneration and unclear nerve cells. CD3-positive lymphocytes and macrophage infiltration from the subarachnoid space into the Virchow-Robin space with widespread white matter edema and spongiosis were
observed, but other immunostaining findings were unclear. The autopsy results suggested GVHD (Fig. 2).

**Discussion**

To diagnose CNS-GVHD, other potential causes of neurological symptoms, such as infections, autoimmune disease, vascular disease, and recurrence of primary disease, must be ruled out through physical and neurological examinations, imaging (MRI/computed tomography), electroencephalograms, electromyograms, and cerebrospinal fluid examinations. The 2009 Consensus Conference on Clinical Practice for chronic GVHD suggest that CNS-GVHD exists when the following six diagnostic criteria or criteria [1], [2], plus two or more of [3] to [6] are satisfied: [1] chronic GVHD affecting other organs, [2] central neurological symptoms not explained otherwise, [3] MRI findings corresponding to the symptoms, [4] abnormal cerebrospinal fluid findings, [5] GVHD findings through a brain biopsy or post-mortem biopsy, and [6] response to immunosuppressive therapy (3, 4). In the present case, criteria [2], [3], and [5] were satisfied, but no response to immunosuppressive therapy was observed; therefore, these diagnostic criteria were not met.

Symptoms of CNS-GVHD are diverse and non-specific, including convulsions, consciousness-related symptoms, motor and sensory symptoms, dysarthria, aphasia, weakness, and paralysis. Histologically, the infiltration of CD8-positive T cells around the cerebrovascular areas rather than that of CD4-positive T cells is often observed, and although such observations aid in diagnosing CNS-GVHD, they cannot confirm the diagnosis if present alone. A high-dose steroid trial may be performed to make a therapeutic diagnosis (4).

We searched the keywords “central nervous system” and “GVHD” in PubMed and selected English articles covering case reports published between 1990 and 2020. A total of 42 cases of CNS-GVHD have been reported so far. The median age was 36 years old (range, 7-68 years old), and the median time of the onset was 390 days (range, 7-7,300 days).

**Figure 1.** Magnetic resonance imaging findings (fluid-attenuated inversion-recovery). (A) Day 34: a high-frequency signal was observed in the occipital white matter. (B) Day 63: extension of the high-frequency signal to the corpus callosum/pons was observed. (C) Day 83: the high-frequency signal in the occipital lobe had expanded further and extended to the frontal lobe.

**Figure 2.** Central autopsy pathological findings. (A) Hematoxylin and Eosin (H&E) staining, low power (10×): congestion and perivascular inflammatory cell infiltration in the cerebral cortex and edema in the white matter were observed. (B) H&E staining, high power (40×): cell infiltration was observed in the Virchow-Robin cavity around the cortical blood vessels. (C) Immunostaining for CD3: infiltration by CD3-positive T cells was observed.
| Reference | Age (years) | Gender | Primary disease | Transplant type | MAC/ RIC | TBI dGVHD | Severity | GVHD Severity | Status (primary disease) | Symptoms/disorders | MR-LWMH location | CSF Findings | Tissue infiltration | Treatment | Response | Outcome |
|-----------|-------------|--------|----------------|----------------|----------|-----------|----------|--------------|----------------------|------------------|------------------|-------------|------------------|-----------|---------|---------|
| 9         | 32          | M      | CML MRD        | NR              | NR       | +         | IV       | +            | NR                   | Others            | NR               | +           | Prostate, cell count increase | NA        | NA      | Death   |
| 10        | 9           | M      | AA MRD         | NR              | NR       | +         | 240 D    | -            | NR                   | Others            | NR               | +           | Prostate, cell count increase | NA        | NA      | Death   |
| 13        | F           | ALL    | F RIC         | NR              | NR       | +         | 17 D     | +            | Cerebrum            | Others            | NR               | +           | Prostate, cell count increase | NA        | NA      | Death   |
| 11        | 14          | F      | LBL MRD        | MAC              | +        | +         | II       | NR           | Cerebrum            | Consciousness disorder, paralys | -               | Prostate, cell count increase | Steroids, Cyclophosphamide | PD       | Death   |
| 12        | 43          | M      | MCL NR         | NR              | NR       | +         | 28 M     | +            | Cerebrum            | Paralys, others       | -               | Prostate, cell count increase | Steroids, Cyclophosphamide | PD       | Death   |
| 14        | F           | AML    | NR            | NR              | NR       | +         | 31 M     | +            | Cerebrum            | Paralys, others       | -               | Prostate, cell count increase | Steroids, Cyclophosphamide | PD       | Death   |
| 19        | M           | ALL    | NR            | NR              | NR       | +         | 5 M      | -            | Cerebrum            | Others             | -               | Prostate, cell count increase | Steroids, Cyclophosphamide | LD       | Lived   |
| 25        | F           | ALL    | UD RIC        | +                | +         | II       | MD       | +            | Cerebrum            | Paralys, others       | -               | Prostate, cell count increase | Steroids, Cyclophosphamide | PD       | Death   |
| 18        | F           | ALL    | UD MRD        | MAC              | NR       | +         | NR       | NR           | Cerebrum            | Paralys, others       | -               | Prostate, cell count increase | Steroids, Cyclophosphamide | PD       | Death   |
| 26        | M           | NHL    | NR(PB) RIC    | +                | +         | II       | +         | 3 Y          | Cerebrum            | Others             | -               | Prostate, cell count increase | Steroids, MMF   | PD       | Death   |
| 23        | F           | FL     | CB RIC        | -                | NR       | -         | 12 M     | +            | Cerebrum            | Consciousness disorder, paralys | -               | Prostate, cell count increase | Steroids, Broadspec PD | Death   |         |
| 24        | M           | CML    | MUD            | NR              | NR       | +         | Moderate  | 4 Y          | Cerebrum            | Others             | -               | Prostate, cell count increase | Steroids, Cyclophosphamide | CR      | Lived   |
| 28        | F           | AML    | MUD NR        | +                | Moderate  | 2 Y       | CR       | Motor impairment, paralys, others | Cerebrum         | Prostate, cell count increase | Steroids, Cyclophosphamide | CR      | Lived   |
| 20        | M           | SCID   | haplo           | 20 Y           | CR       | Motor impairment, paralys, others | Cerebrum         | Prostate, cell count increase | Steroids, Cyclophosphamide | CR      | Lived   |
| 33        | M           | CLL    | MUD            | NR              | NR       | +         | Moderate  | 2 Y          | Motor impairment, convulsions, paralys, others | Cerebrum         | Prostate, cell count increase | Steroids, Cyclophosphamide | PD      | Death   |
| 25        | M           | MML    | MUD            | MAC              | -        | -         | 4 W      | CR           | Paralys, others       | Cerebrum, Lymphocytosis | Prostate, cell count increase | Steroids, Cyclophosphamide | CR      | Lived   |
| 26        | M           | CLL    | MUD            | MAC              | +        | +         | 92 C     | CR           | Motor impairment, others | Cerebrum, Lymphocytosis | Prostate, cell count increase | Steroids, Cyclophosphamide | CR      | Lived   |
| 27        | M           | AA     | MRD            | RIC              | +        | +         | 31 M     | CR           | Convulsions, others | Cerebrum, Lymphocytosis | Prostate, cell count increase | Steroids, Cyclophosphamide | CR      | Lived   |
| 35        | F           | MCM    | RIC            | +                | +         | Severe 308 D | CR       | Motor impairment, others | Cerebrum, Lymphocytosis | Prostate, cell count increase | Steroids, Cyclophosphamide | CR      | Lived   |
| 62        | F           | MCM    | MUD            | MAC              | +        | +         | 19 D     | CR           | Consciousness disorder, paralys | Cerebrum, Lymphocytosis | Prostate, cell count increase | Steroids, Cyclophosphamide | CR      | Lived   |
| 29        | F           | Fanconi | CB RIC        | -                | +         | Severe 378 D | CR       | Others       | Cerebrum            | Prostate, cell count increase | Steroids, Cyclophosphamide | CR      | Lived   |
| 25        | M           | MPN    | UD MAC         | -                | +         | Moderate  | 259 D    | NR           | Others             | Multiple areas, cerebellum | -               | Prostate, cell count increase | Steroids, Cyclophosphamide | CR      | Lived   |
| 36        | M           | MCM    | MRD            | NR              | +         | Moderate  | 119 D    | NR           | Paralys, others       | Cerebrum, Lymphocytosis | Prostate, cell count increase | Steroids, Cyclophosphamide | CR      | Lived   |
| 60        | M           | AML    | 2nd RIC       | +                | -         | 7 D      | CR           | Consciousness disorder, paralys | Cerebrum, Lymphocytosis | Prostate, cell count increase | Steroids, Cyclophosphamide | CR      | Lived   |
| 35        | M           | FDS    | MUD RIC       | -                | +         | Mild 24 M | CR           | Convulsions, others | Cerebrum, Lymphocytosis | Prostate, cell count increase | Steroids, Cyclophosphamide | CR      | Lived   |
| 68        | M           | MDS    | UD RIC        | +                | -         | 742 D    | CR           | Others       | Cerebrum            | Prostate, cell count increase | Steroids, Cyclophosphamide | CR      | Lived   |
| 44         | M           | MDS    | 2nd RIC       | +                | +         | Moderate  | 24 D     | CR           | Consciousness disorder, paralys | Cerebrum, Lymphocytosis | Prostate, cell count increase | Steroids, Cyclophosphamide | PD       | Death   |

M: male; F: female, D: day, M: month, Y: year, AML: acute myeloid leukemia, ALL: acute lymphoblastic leukemia, CML: chronic myeloid leukaemia, CLL: chronic lymphocytic leukemia, MDS: myelodysplastic syndrome, MPN: myeloproliferative neoplasms, CMML: chronic myelomonocytic leukemia, NHL: non-Hodgkin lymphoma, LBL: lymphoblastic lymphoma, FL: follicular lymphoma, AA: aplastic anemia, TCL: T cell lymphoma, SCID: severe combined immunodeficiency, MRD: matched related donor, MUD: matched unrelated donor, UD: unrelated donor, Haplo: haploidentical donor, CR: cord blood, WMH: white matter hyperintensity, MAC: myeloablative conditioning, RIC: reduced intensity conditioning, TBI: total body irradiation, dGVHD: acute graft-versus-host disease, gGVHD: chronic graft-versus-host disease, MR/MPR: magnetic resonance imaging, IVG: intravenous immunoglobulin, MMF: mycophenolate mofetil, CSF: cerebrospinal fluid, CR: complete response, PR: partial response, PD: progressive disease, No R: no response, NR: not reported, NA: not available, Ov: others: involuntary movements, weakness, sensory disorders, visual impairment, muscle weakness, personality changes, extrapyramidal symptoms, cerebellar symptoms, polymyositis, memory disorders, depression, vertigo, cognitive disorders, urinary retention, visual impairment, dysthria, hearing impairment, epileptic seizures, tinnitus, headache, cerebellar symptoms, aplasia.
days) after transplantation. Acute and chronic GVHD other than CNS-GVHD were observed in 87.5% (35/40) of cases. Symptoms varied, but convulsions (23.2%) and consciousness-related symptoms (18.6%) were common. Abnormal findings on MRI included gross lesions and multiple white matter lesions in almost all cases [92.9% (39/42)]; in 57.1% of the cases, lesions were found in the cerebral white matter. A cerebrospinal fluid examination showed increased protein levels and cell counts in 57.9% (22/38) and 26.3% (10/38) of cases, respectively. A histological examination might potentially have yielded the most important findings for a diagnosis, but it was performed in only 46.5% (20/44) of the cases. A biopsy revealed perivascular lymphocyte infiltration (inflammation) in 76.2% (16/21) of cases. The treatment used included steroids (1.5-2.0 mg/kg) (92.3%), and the response rate (partial remission+remission) was relatively high (77.5%, 31/40), with a remission rate of 37.5% (15/40). Only one case entered remission without the use of steroid drugs, and all seven steroid-refractory cases were fatal. The mortality rate was 55.3% (21/38) due to subsequent complications, such as relapse and infection, and the prognosis was poor (Table) (4-27).

In the present case, neurological and serological tests were performed, but the actual cause was unclear. Although all of the drugs were changed, there was no improvement, and it was deemed to be a case of CNS-GVHD based on an exclusion diagnosis and post-mortem pathological autopsy results. Histological findings are also important in the diagnosis, and a brain biopsy should also be considered during the course of the disease. As with other types of GVHD, the use of steroids is vital in the treatment of CNS-GVHD, and responsiveness to steroids is integral in its diagnosis and prognostic assessment. In cases with steroid resistance, aside from tacrolimus and cyclosporin, which are usually used for GVHD prevention, anti-thymocyte globulin and cyclophosphamide as well as new GVHD treatments, such as mesenchymal stem cells and Janus kinase (JAK) inhibitors, are also options. Although no drugs have yet been reported to be effective when administered intrathecaally, the existence of the blood-brain barrier in the CNS means it is necessary to consider direct administration via the CSF and to select drugs with consideration of their CNS permeability in cases with abnormal CSF findings. Understanding the laboratory findings and clinical features and characteristics of CNS-GVHD may lead to earlier therapeutic intervention and the prevention of exacerbation; further studies are thus needed in the future.

The authors state that they have no Conflict of Interest (COI).

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