1. Introduction

Guillain–Barré syndrome (GBS) is an acute neurological disorder that is characterized by rapid progressive, symmetrical weakness of the extremities. GBS consists of at least 4 subtypes of acute peripheral neuropathy, of which the most common form is acute inflammatory demyelinating polyneuropathy (AIDP) [1].

Peripheral neuropathy is an uncommon complication of allogeneic bone marrow transplantation (BMT) and 4% of cases develop neuropathy within the first 3 months after BMT [2]. Most peripheral neuropathies after allogeneic BMT are of the AIDP subtype [2–6], possibly due to the increased susceptibility to infections and defects in both cell-mediated and humoral immunity. AIDP typically occurs in the clinical setting of graft-versus-host disease (GVHD) where immunologically competent donor T-cells and/or autoantibodies attack host tissues [2]. However, the number of patients and neuropathological evaluations reported to date are too limited to suggest specific regimens for treatment.

Here, we report a patient with GBS whose neurophysiological findings revealed an AIDP pattern and whose pathological findings confirmed infiltration of macrophages and CD8+ T-cells caused by immune-mediated mechanism related to GVHD. He was effectively treated using 3 rounds of intravenous immunoglobulin and had a good prognosis.

2. Materials and methods

2.1. Neuropathology

Right sural nerve biopsy was performed 41 days after the onset of neurological symptoms. The specimen was divided into 2 portions. One portion was fixed in 2.5% glutaraldehyde in 0.125 M cacodylate buffer (pH 7.4) and embedded in epoxy resin for morphometric and ultrastructural studies. The density of myelinated fibres was assessed using toluidine blue staining. Another fraction was processed for a structural study. The second portion of the specimen was fixed in 10% formalin and paraffin embedded. Following sectioning, the tissue was stained with haematoxylin and eosin and the Kluver–Barrera method. Immunohistochemical studies were performed on consecutive, deparaffinised sections using the following antibodies: mouse monoclonal anti-CD4, anti-CD8, anti-CD68, and anti-CD20 (Dako).

Abbreviations: Ara-C, cytarabine; BU, busulfan; HDAC, high-dose cytarabine; IDA, idarubicin; MTX, methotrexate; PSL, prednisolone.

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2.2. Literature review

Two independent investigators (YT and YU) searched PubMed on January 20, 2016, using the term “allogenetic bone marrow transplantation”, “hematopoietic stem cell transplantation” AND each of the following terms: “Guillain-Barre syndrome”, “neuropathy” and “neurological complication”. Only papers written in English were included. Additional articles were sourced manually by searching the citations of relevant articles. We included 10 full-text articles that described patients who developed GBS after BMT [3–12] (Table 1) and 2 clinical review articles [13,14].

3. Case report

A 50-year-old man was diagnosed with acute myelogenous leukemia (FAB M0 with a complex chromosomal anomaly). Following induction chemotherapy (IDA and Ara-C), 3 cycles of consolidation therapy (cyclophosphamide and BU), an allogeneic BMT was performed with his HLA-matched older brother acting as donor. As prophylaxis for GVHD, cyclosporine and MTX were administered. On day 68 after BMT, he presented erythema exudative multiforme, which he complained of numbness in his distal upper and lower extremities. Neurological examination revealed complete sensory loss in his distal upper and lower extremities. As a treatment of GBS, we also considered plasma exchange. He showed hyperesthesia in his distal upper and lower extremities.

Serological tests revealed no abnormalities. Although serological markers for Epstein–Barr virus, herpes simplex virus (HSV), varicella-zoster virus (VZV), HIV, mycoplasma, listeria, and Campylobacter jejuni were negative, pp65 cytomegalovirus (CMV) antigenemia was positive (14/50,000 cells). We repeated tests for CMV antigenemia once a week; and the tests became negative after the use of ganciclovir for 1 month after the onset of neurological symptoms. His anti-ganglioside antibodies, including GM1IgG, were all negative. His cerebrospinal fluid (CSF) showed a mild increase in cells (19/μl) and an elevation in protein levels (118 mg/dl). Polymerase chain reaction on the CSF was also negative for HSV, VZV, and CMV both at the onset of neurological symptoms and 1 month thereafter. Two days after the onset of neurological symptoms, nerve conduction studies showed delayed motor nerve conduction velocity (left median nerve: 31.7 m/s, ulnar nerve: 41.8 m/s, tibial nerve: 24.8 m/s) with temporal dispersion and decreased amplitude of compound muscle action potential (left median nerve: 420 μV, ulnar nerve: 640 μV, tibial nerve: 230 μV). F waves and sensory nerve action potentials could not be evoked. His cervical and lumbosacral MRI showed no abnormal lesions.

In semi-thin cross sections, the total myelinated fibre densities were moderately decreased (Fig. 1a). Myelin ovoids and endoneurial oedema were observed. There was no evidence of vasculitis or abnormal deposits. Teased-fibre studies showed that the frequency of segmental demyelination and axonal degeneration was 30.4% and 15.2%, respectively (Fig. 1b). Scattered lymphocytes and numerous macrophages were detected in the parenchyma. Immunohistochemical studies confirmed infiltration of CD8-positive cytotoxic T-cells and CD68-positive macrophages (Fig. 1c and d). These neurophysiological and pathological findings were compatible with the diagnosis of AIDP.

The patient was treated with 2 courses of intravenous immunoglobulin (IVIG, 400 mg/kg per day) for 5 days; however, his symptoms remained unchanged. As a treatment of GBS, we also considered plasma exchange. We included 10 full-text articles that described patients who developed GBS after BMT [3–12] (Table 1) and 2 clinical review articles [13,14].

Table 1

| Age/gender | Tumor | GVHD (at the time of BMT) | GBS on set after BMT | CMV antignenemia | Treatment | Outcome | Cause |
|------------|-------|---------------------------|----------------------|------------------|-----------|---------|-------|
| 50/male    | AML   | Chronic GVHD              | 114 days (+)         | -                | IVIG      | Recovery | GvHD > CMV |
| 64/male    | WM    | Unclear                   | -                     | -                | IVIG, rituximab | Alive   |                   |
| 59/male    | AML   | Unclear                   | -                     | -                | IVIG      | Not known |                   |
| 37/male    | AML   | Unclear                   | -                     | -                | IVIG, rituximab | Alive   |                   |
| 44/female  | MDS   | Unclear                   | -                     | -                | IVIG      | Alive    |                   |
| 58/female  | NHL   | Unclear                   | -                     | -                | Steroids, IVIG, plasmapheresis, cyclosporin | Recovery following cyclosporin |                   |
| 58/male    | MDS   | Possible chronic GVHD     | 69 days (-)           | -                | IVIG, rituximab, steroids, IVIG, cyclosporin, plasmapheresis | Alive |                   |
| 34/female  | ALL   | Acute GVHD                | 78 days (+)           | -                | IVIG      | Recovery |                   |
| 40/female  | CML   | Acute GVHD                | -                     | -                | IVIG      | Partial initial improvement |                   |
| 18–60      | MDS   | Chronic GVHD              | 142 days (+)          | -                | IVIG, rituximab, plasmapheresis | Death following respiratory failure |                   |
| 18–60      | AML   | Possible chronic GVHD     | 101 days (+)          | -                | IVIG, rituximab, plasmapheresis | Death following respiratory infection |                   |
| 16/male    | T cell ALL |                | 6 days (-)            | -                | IVIG      | Death    | Ara-C treatment prior to transplantation |
| 17/male    | T cell Lymphoma            | 3 days (-)            | -                | -                | IVIG      | Death    | Ara-C treatment prior to transplantation |
| 18/male    | T cell ALL |                | 2 days (-)            | -                | IVIG      | Death    | Ara-C treatment prior to transplantation |
| 34/female  | CML   | No GVHD                   | 120 days (-)          | -                | IVIG      | Improvement |                   |
| 27/male    | HD    | No GVHD                   | 450 days (-)          | -                | IVIG      | Recovery |                   |
| 34/male    | AML   | Mild GVHD                 | 120 days (-)          | -                | IVIG      | Improvement |                   |
| 59/female  | MLD   | Mild GVHD                 | 330 days (+)          | -                | IVIG, plasmapheresis | Death |                   |
| 43/male    | AML   | Acute GVHD                | 163 days (-)          | -                | IVIG, plasmapheresis | Death |                   |
| 23/male    | AML   | No GVHD                   | 42 days (-)           | -                | IVIG, plasmapheresis | Death |                   |

GVHD—graft versus host disease; BMT—bone marrow transplant; CVM—cytomegalovirus; AML—acute myeloid leukemia; CML—chronic myeloid leukemia; MDS—myelodysplastic syndrome; NHL—Non-Hodgkin’s Lymphoma; HD—Hodgkin’s disease; WM—Waldenstrom macroglobulinemia; ALL—acute lymphoblastic leukemia; IVIG—intravenous immunoglobulin.
exchange (PE), given the severity of his motor symptoms. However, since his general status was not good and he presented thrombocyto-
penia (PLT 27–58 × 10^3/μl), we decided against PE. Muscle strength gradually improved after the third round of IVIG therapy, and ventilator weaning was possible at 86 days after the onset of neurological symp-
toms. He was able to walk with assistance 130 days after the onset of neurological symptoms, and eventually regained the ability to walk without assistance.

4. Discussion

We here reported on a male patient who developed severe peripheral neuropathy at the time of recovery from acute GVHD after allogenic BMT, when immunosuppression therapy was gradually attenuated. Although symptoms of acute GVHD, such as erythema exudative multiforme and diarrhoea had improved, neurological symptoms presented on day 114 after BMT. Based on the diagnostic criteria of acute and chronic GVHD, he was diagnosed with overlap syndrome since the neurological symptoms newly occurred more than 100 days after BMT [15]. Toxins, infection, and critical illness polyneuropathy were ex-
cluded as causes in the present case and neurophysiological and neuro-
pathological findings were compatible with a diagnosis of AIDP. He was successfully treated with 3 rounds of IVIG.

Peripheral neuropathy appears to be a rare complication of BMT that can develop as early as 2 days and up to 15 months after BMT [3,7]. Wen et al. reviewed several studies that reported the presentation of GBS follow-
ing allogenic BMT and proposed several mechanisms for the patho-
genesis of GBS after BMT including the development of an aberrant immunological response to infections, drug toxicity, and a possible manifestation of GVHD [3]. Fujisaki proposed that the mechanism of GBS after allogenic BMT was not direct neural involvement by CMV and humorally mediated cross-reaction, but rather peripheral expan-
sion of T-cells following CMV infection [5]. We reviewed the recent de-
velopments in the field in order to better understand the pathogenesis of GBS following BMT (Table 1).

Previous studies found that 6 of 11 patients were positive for serologi-
cal markers of Campylobacter jejuni or CMV and 4 of these 6 patients presented with some form of GVHD [3]. One study of 85 patients report-
ed that 3 patients with GBS after BMT, who presented with EBV or CMV infection, 1 of which was diagnosed with GVHD [4]. Peripheral neuropa-
thy has been shown to occur in the clinical course of GVHD. In 1 case, an allogeneic BMT patient developed GBS as the leading manifestation of GVHD subsequent to discontinuation of immunosuppressive medication with cyclosporine; resumption of immunosuppressive medication im-
proved the patient's condition [6]. In the present study, the symptoms developed almost 6 months after chemotherapy and biopsy results indi-
cated GVHD, which was then treated with immunosuppression therapy. Since it occurred during the timing when PSL as a treatment of acute GVHD was reduced, an immune-mediated mechanism related to GVHD seemed plausible. In addition, while the titre was low and there were no symptoms of viral infection, the patient was positive for the CMV an-
tigen and these tests became negative at 1 month after starting treat-
ment with ganciclovir. We cannot totally exclude the involvement of CMV infection as a factor of GBS in the present patient. Therefore, an im-
une-mediated mechanism related to GVHD, and to some extent, CMV infection, appeared to be the most likely cause of GBS in the present case.

While many histopathological studies have been performed for GBS cases after BMT, only 2 studies have performed immunohistochemical analysis on sural nerve biopsies. In 1 case, an axonal type of GBS was preceded by CMV infection without clinical symptoms of GVHD, where axonal loss and infiltration of plasma cells was detected [4]. In the other case, the axonal type of GBS was preceded by CMV infection after acute GVHD and infiltration of CD8+ T-cells and macrophages were detected [5]. Similarly, in our study, CD8 + T-cell and macrophage infiltration were detected along with active demyelinating patterns and axonal degeneration. Thus, our results suggest that CD8 + T-cell activation may play an important role in the pathophysiology of GBS at the time of recovering from acute GVHD after BMT.

Most patients who develop GBS post-transplant recover after treat-
ment with IVIG and/or PE [3,8]. Usually, neurological symptoms gradu-
ally improve within 1 to several months after these treatments [3,11]. In 1 report, although muscle strength remained unchanged after IVIG by day 88 after neurological symptom onset, the patient displayed rapid recovery of muscle strength by day 150 [5]. In some cases, the
combination of IVIG and rituximab appeared to have a better outcome [8,9]. Thone et al. have reported 1 case of GBS after BMT who was treated with cyclosporine after a poor response to IVIG and PE [6]. In that case, the patient required artificial ventilation at 18 days after the neurological symptom onset. Following cyclosporine treatment initiation at day 26, his symptoms improved markedly and he was weaned off artificial ventilation by 14 days later. However, in a case report of GBS associated with CMV infection after allogeneic hematopoietic stem cell transplantation and in a review of GBS after allogeneic hematopoietic stem cell transplantation, the outcome of GBS was poor, and all patients (n = 4) died after respiratory and/or multisystem failure 1–5 months after transplant [12,13]. In the present study, the patient was treated with cyclosporine, MTX, as well as PSL for GVHD. While the GVHD symptoms, such as severe diarrhoea and mild skin rash, improved with this approach, the GBS symptoms persisted. After treatment with repetitive IVIG, his prognosis was good. Since the mechanism of GBS after allogeneic BMT may vary, a combined treatment approach of treating infection and GVHD with IVIG and/or PE seems to be effective. Several rounds of IVIG may be useful for severe forms of GBS after allogeneic BMT.

Conflict of interest

The authors declare that there are no conflicts of interest.

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