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Case report

Guillain–Barré syndrome after allogeneic bone marrow transplantation: Case report and literature review

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ABSTRACT

A 50-year-old man with acute myelogenous leukemia underwent allogeneic bone-marrow transplantation (BMT). He presented with severe diarrhoea 86 days post BMT and was diagnosed with graft-versus-host disease (GVHD) based on skin and rectal biopsies. He complained of numbness and weakness in the distal extremities at 114 days after BMT. His symptoms rapidly deteriorated and he required mechanical ventilation for respiratory failure. His clinical course and the findings of a nerve conduction study fulfilled the criteria for diagnosis of Guillain–Barré syndrome (GBS). Sural nerve biopsy revealed active demyelination and infiltration of macrophages and $CD8^+$ T-cells. After three cycles of intravenous immunoglobulin therapy, his symptoms gradually improved, and he could eventually walk unassisted. Although GBS has been known to develop after allogeneic BMT, the pathogenesis remains unclear, and specific treatment regimens have not been well established. Here, we report a case of GBS, caused by an immune-mediated mechanism related to GVHD, which was successfully treated using intravenous immunoglobulin therapy.

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 polyradiculoneuropathy (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 finding 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 teased-fibre 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 "allogeneic 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 (HDAC), intrathecal chemotherapy (MTX, Ara-C, and PSL) and conditioning chemotherapy (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, followed by severe diarrhoea on day 86, and was diagnosed with acute GVHD (Grade III) based on skin and rectal biopsies. After he was treated with PSL (60 mg; 1 mg/kg bodyweight), his symptoms gradually improved to Grade II, and the dosage of PSL was gradually reduced to 20 mg. The neurological symptoms began on day 114 after BMT where he complained of numbness in his distal upper and lower extremities and difficulty in swallowing. The weakness of his extremities rapidly increased and on day 116 he required mechanical ventilation for respiratory failure. Neurological examination revealed complete tetraplegia and absence of deep tendon reflexes. 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) antigenaemia was positive (14/50,000 cells). We repeated tests for CMV antigenaemia 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 lumber 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 de/remyelination 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

Table 1
Analysis of the patients who developed GBS after allogeneic BMT.

Age/gender	Tumor	GVHD (at the time of GBS)	GBS on set after BMT	CMV antigenomia	Treatment	Outcome	Cause
50/male	AML	Chronic GVHD	114 days	(+)	IVIg	Recovery	GVHD > CMV
64/male	WM	Unclear		(−)	IVIG	Alive	
59/male	AML	Unclear		(−)	IVIG, rituximab	Not known	
37/male	AML	Unclear		(−)	IVIG	Alive	
44/female	MDS	Unclear		(+)	IVIG, rituximab	Alive	
58/female	NHL			(−)	Steroids, IVIG, plasmapheresis, cyclosporin	Recovery following cyclosporin	Discontinuation of immunosuppressant, GVHD
58/male	MDS	Possible chronic GVHD	69 days	(−)	IVIG, rituximab, steroids	Alive	Possible GVHD
34/female	ALL	Acute GVHD	78 days	(+)	IVIG, cyclosporin	Recovery	Immune-mediated
40/female	CML	Acute GVHD			Steroids, cyclosporin, IVIG, plasmapheresis	Partial initial improvement but ultimate death	GVHD
18–60	MDS		142 days	(+)	IVIG	Death following respiratory failure	
18–60	NHL	Chronic GVHD	160 days	(+)	IVIG, rituximab, plasmapheresis	Death following respiratory infection	
18–60	AML	Possible chronic GVHD	101 days	(+)	No specific treatment	Death following respiratory failure	
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		Plasmapheresis	Improvement	
27/male	HD	No GVHD	450 days		Plasmapheresis	Recovery	
34/male	AML	Mild GVHD	120 days		Plasmapheresis	Improvement	
59/female	CML	Mild GVHD	330 days	(−)	IVIG, plasmapheresis	Death	
43/male	CML	Acute GVHD	163 days	(+)	IVIG, plasmapheresis	Very slight neurological deficiency	HHV-6
23/male	AML	No GVHD	42 days		IVIG, plasmapheresis	Death	CMV

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.