Hematol Oncol Stem Cell Ther (2019) 12, 110–114

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/hemonc

CASE REPORT

# Myasthenia gravis after allogeneic bone marrow transplantation: A case report and literature review

Yutaka Tsutsumi [a,*], Takashi Kamiishi [a], Ryo Kikuchi [a], Shinichi Ito [a], Satomi Matsuoka [a], Takanori Teshima [b]

[a] Department of Hematology, Hakodate Municipal Hospital, Hakodate, Japan
[b] Department of Hematology, Hokkaido Graduate School of Medicine, Sapporo, Japan

Received 3 December 2016; accepted 25 April 2017
Available online 18 May 2017

KEYWORDS
Acetylcholine receptor antibody;
Allogeneic stem cell transplantation;
Chronic GVHD;
Myasthenia gravis

**Abstract**
A 52-year-old man with acute myeloid leukemia underwent allogeneic hematopoietic stem cell transplantation and developed extensive chronic graft-versus-host disease and myasthenia gravis (MG), which became involved with oculobulbar and proximal upper and lower limb weakness in 677 days. In the literature, we identified 24 cases where MG developed after allo-SCT. Graft-versus-host disease development and male recipients of female donors might be prone to the development of posttransplant MG (odds ratio, 3.75).


## Introduction

Myasthenia gravis (MG) is an autoimmune neuromuscular disorder caused by antibodies (Abs) against acetylcholine receptors (AChRs). Smith et al. [1] reported that even though 20% of chronic graft-versus-host disease (cGVHD) patients were positive for anti-AChR Abs, MG development is rare after allogeneic hematopoietic stem cell transplantation (allo-HCT). Here, we report a case of a posttransplant MG which showed the AChR and cGVHD changes over time from HCT and review similar case reports in the literature.

## Materials and methods

We retrospectively measured the serum levels of the AChR Abs of the patient's frozen serum samples. For the AChR analysis, we used the AChR autoantibody RIA kit (RiaRSRTM AChR Ab; RSR Limited, Cardiff, UK) based on the manufac-

* Corresponding author at: Department of Hematology, Hakodate Municipal Hospital, 1-10-1, Minato-Cho, Hakodate 041-8680, Japan.
*E-mail address:* yutsutsu@shore.ocn.ne.jp (Y. Tsutsumi).

http://dx.doi.org/10.1016/j.hemonc.2017.04.001

turer's recommendations. Previous reports were located by PubMed, and statistical analysis was performed with StatMate V software (ATMS Co., Ltd., Tokyo, Japan). This analysis was approved by the Institutional Review Board of Hakodate Municipal Hospital, Hakodate, Japan, and we obtained informed consent of the preservation of the serum samples at the patient's admission.

## Case report

A 52-year-old male with acute myelogenous leukemia underwent allogeneic bone marrow transplantation (BMT) from an human leukocyte antigen (HLA)-identical (HLA, A 24:02, 24:20, B 52:01, 55:02, Cw 01:02, 12:02, DR 09:01.15:02) unrelated donor. The conditioning regimen was 3.2 mg/kg of busulfan for 4 days and 60 mg/kg of cyclophosphamide for 2 days. The GVHD prophylaxis was a combination of short-term methotrexate and tacrolimus (FK 506). The clinical course of this case is shown in Fig. 1. On Day 17 after BMT, neutrophil engraftment was achieved, and skin Stage 2, Grade I acute GVHD (aGVHD) developed. Although the GVHD was successfully treated with 30 mg of prednisone (PSL), cGVHD, which involves the skin, the oral cavity, the liver, and the lungs, developed after discontinuation of PSL. Treatment with 20 mg of PSL ameliorated the cGVHD. The patient presented with oculobulbar and proximal upper and lower limb weakness 677 days posttransplantation. Our diagnosis of MG was performed by a neurologist, based on the positivity of the AChR Abs and a waning electromyography pattern with a positive edrophonium test. The patient had no thymoma. The administration of 1 g of methylprednisolone sharply decreased the serum levels of the AChR Abs, but muscle deterioration accelerated. Even though the administration of intravenous immunoglobulin was partially effective, the patient died of cholangitis and sepsis on Day 790 after BMT without an acute myelogenous leukemia relapse. We retrospectively measured the serum levels of the AChR Abs of the patient's frozen serum samples (3 days and 615 days posttransplantation). The AChR Abs, which were negative before and soon after the allo-BMT, became positive 3 months before the onset of MG.

## Literature review

We reviewed 24 cases that developed myathenia gravis (MS) after allo-HCT (Table 1) [2—22]. Our analysis is based on several case reports, which unfortunately, were incomplete. Their median age was 20 years, and MG more frequently developed in the male recipients of female donors

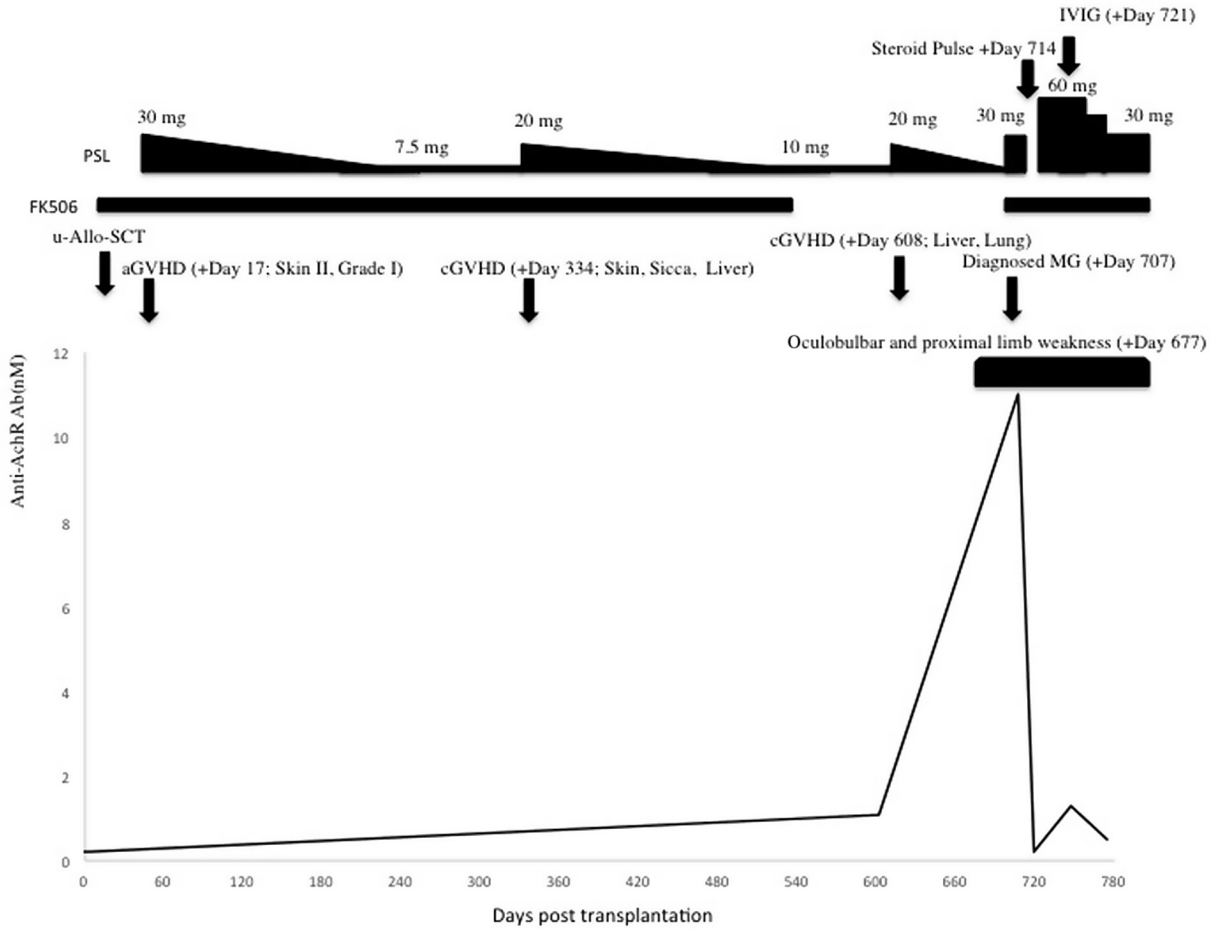


**Fig. 1** Clinical course of case after hematopoietic stem cell transplantation. Myasthenia gravis (MG) developed after the reduction in prednisolone for chronic graft-versus-host disease (cGVHD) treatment.

**Table 1** Patient characteristics.

| | | |
|---|---|---|
| Age | | 20 (0.5—54) |
| Recipient/donor | | |
| | Male/male | 2 |
| | Male/female | 10 |
| | Female/male | 3 |
| | Female/female | 4 |
| Gender | | |
| | Match | 6 |
| | Mismatch | 13 |
| Disease | | |
| | AML | 4 |
| | CML | 6 |
| | ALL | 1 |
| | AA | 8 |
| | NHL | 3 |
| | SCID | 2 |
| | Griscelli | 1 |
| Conditioning | | |
| | BU + CY | 3 |
| | BU + CY + TBI | 1 |
| | CY | 2 |
| | CY + TBI | 4 |
| | AraC + CY + TBI | 1 |
| | CY + ATG | 2 |
| | N/A | 12 |
| Donor source | | |
| | Sibling | 15 |
| | Grandmother | 1 |
| | Unrelated | 2 |
| | N/A | 7 |
| HLA compatibility | | |
| | Match | 13 |
| | Mismatch | 5 |
| | N/A | 7 |

AA = aplastic anemia; ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; AraC = cytarabine; ATG = antithymocyte globulin; BU = busulfan; CML = chronic myeloid leukemia; CY = cyclophosphamide; NHL = nonHodgkin lymphoma; SCID = severe combined immunodeficiency; TBI = total body irradiation.

**Table 2** Graft-versus-host disease (GVHD) and treatments.

| | | |
|---|---|---|
| aGVHD | | |
| | Present | 14 |
| | Absent | 3 |
| | N/A | 6 |
| cGVHD | | |
| | Present | 21 |
| | Absent | 2 |
| | N/A | 1 |
| | (Limited) | 2 |
| | (Extensive) | 12 |
| cGVHD treatment | | |
| | CsA | 2 |
| | CsA + PSL | 9 |
| | CsA + PSL + MMF | 1 |
| | FK + PSL | 1 |
| | PSL + AZT | 7 |
| | N/A | 4 |
| | (Taper or stop) | 18 |
| Relapse | | |
| | No | 16 |
| | N/A | 8 |

aGVHD = acute GVHD; AZT = azathioprine; cGVHD = chronic GVHD; CsA = cyclosporin; FK = tacrolimus; MMF = mycophenolate mofetil; PSL = prednisone.

(odds ratio, 3.75). Five of these samples were unavailable because the donor gender was not specified. The grandmother was a 1-locus mismatch donor. The HLA-match was almost all HLA identical siblings. The HLA-mismatch was a 1-locus mismatch (7/8 was 3 and 5/6 was 1), and only one patient was a 2-locus mismatch (6/8). The HLA disparity and the type of conditioning regimen features were not conspicuous. GVHD and its treatments are shown in Table 2. Most MG patients had both aGVHD and cGVHD. Before the development of MG, the cGVHD treatments were calcineurin inhibitors plus PSL in 13 patients and azathioprine (AZT) and PSL in seven patients. The proximal extremities were the most often involved sites (22 cases), and more than two lesions were involved in most of the patients (Table 3). The AChR Abs were positive in 19 patients, but muscle-specific kinase Abs were only positive in two. MG was treated with calcineurin inhibitors and a PSL-based regimen in nine patients or with AZT or a mycophenolate mofetil (MMF) and a PSL-based regimen in nine patients. AZT was generally used before 1999. Treatments were at least partly effective in 19 patients.

## Discussion

Even though MG, an Ab-mediated autoimmune disorder of the neuromuscular junction [23], develops after allo-HCT, its incidence is less than 1%.[8] It develops at a median of 24 months posttransplant in a range of 3—100 months, often in association with cGVHD [10,12] and after the discontinuation or the tapering of immunosuppressive drugs. The incidence of AChR Ab positivity might be as high as 40% of the allo-HCT recipients who exhibit no MG symptoms [18,24]. In our case, the AChR Abs were negative soon after the allogeneic HCT, but positive after the development of cGVHD, which is associated with dysregulated B cells and humoral immunity manifested by simultaneous B-lymphocytopenia and B-cell hyperactivity, as well as the production of autoantibodies [25—28].

MG sometimes develops with other autoimmune-like diseases, such as glomerulonephritis and polymyositis [8,13]. Grauer et al. [29] reported the risk of aplastic anemia from the development of MG after allo-HCT. In our literature review, 8/25 patients had aplastic anemia.

MG is associated with the following specific HLAs: HLA-Cw1, Cw7, DR2, DR3, DQ2, and B8 [3]. In our literature research, posttransplant MG was not associated with speci-

**Table 3** Clinical features of posttransplant myasthenia gravis (MG).

| | | |
|---|---|---|
| Duration | | 26 (3—00) |
| Position | | |
| | Ocular | 17 |
| | Bulbar | 13 |
| | Extremities | 21 |
| | 1 lesion | 2 |
| | 2 lesions | 7 |
| | 3 lesions | 13 |
| | N/A | 2 |
| Antibody | | |
| | AChR | 19 |
| | MuSK | 2 |
| | Negative | 2 |
| | N/A | 1 |
| Thymoma | | |
| | Negative | 14 |
| | N/A | 10 |
| Treatment | | |
| | CsA + PSL | 7 |
| | FK + PSL + IVIG | 1 |
| | PSL + plasmapheresis | 1 |
| | PSL | 4 |
| | PSL + AZT | 6 |
| | PSL + AZT + thalidomide | 1 |
| | PSL + MMF | 1 |
| | CsA + MMF + IVIG + PSL + rituximab | 1 |
| | N/A | 2 |
| Pyridostigmine | | |
| | Administer | 18 |
| | None | 3 |
| | N/A | 3 |
| Outcome | | |
| | Improve | 19 |
| | N/A | 5 |
| | Death (infection/gastric ulcer) | 2/1 |

AChR = anti-acetylcholine receptor antibody; AZT = azathioprine; CsA = cyclosporin; FK = tacrolimus; IVIG = intravenous immunoglobulin; MMF = mycophenolate mofetil; MuSK = anti-muscle-specific kinase antibody; PSL = prednisone.

fic HLAs. No patients had thymoma, which is often complicated by idiopathic MG. These results suggest that the etiology of MG's development may differ from idiopathic MG. Almost all of the patients received pyridostigmine bromide and immunosuppressive therapy, both of which are usually effective. Even though more intensive therapies such as plasmapheresis, intravenous immunoglobulin (IVIG), or rituximab were sometimes required, almost all of the post-transplant MG patients improved [21].

## Conflicts of interest

The authors report no conflicts of interest.

## References


[1] Smith CIE, Hammarstrom L, Lefvert AK. Bone marrow grafting induces acetylcholine receptor antibody formation. Lancet 1985;1:978.

[2] Atassi N, Amato AA. Muscle-specific kinase (MuSK) antibody-associated myasthenia gravis after bone marrow transplantation. Muscle Nerve 2008;38:1074—5.

[3] Mackey JR, Desai S, Larratt L, Cwik V, Nabholtz JM. Myasthenia gravis in association with allogeneic bone marrow transplantation: clinical observations, therapeutic implications and review of literature. Bone Marrow Transpl 1997;19:939—42.

[4] Baron F, Sanzot B, Wang F, Beguin F. Myasthenia gravis without chronic GVHD after allogeneic bone marrow transplantation. Bone Marrow Transpl 1998;2:197—200.

[5] Dowell JE, Moots PL, Stein RD. Myasthenia gravis after allogeneic bone marrow transplantation for lymphoblastic lymphoma. Bone Marrow Transpl 1999;24:1359—61.

[6] Kotani A, Takahashi A, Koga H, Morita R, Fukuyama H, Ichinohe T, et al. Myasthenia gravis after allogeneic bone marrow transplantation treated with mycophenolate mofetil monitored by peripheral blood OX40 + CD4 + T cells. Eur J Haematol 2002;69:318—20.

[7] Smith CI, Aarli JA, Biberfeld P, Bolme P, Christensson B, Gahrton G, et al. Myasthenia gravis after bone marrow transplantation. Evidence for a donor origin. N Engl J Med 1983;309:1565—8.

[8] Tse S, Saunders EF, Silverman E, Vajsar J, Becker L, Meaney B. Myasthenia gravis and polymyositis as manifestation of chronic graft-versus-host disease. Bone Marrow Transpl 1999;23:397—9.

[9] Yanagihara C, Nakaji K, Tanaka Y, Yabe H, Nishimura Y. A patient of chronic graft-versus-host disease presenting simultaneously with polymyositis and myasthenia gravis. Rinsho Shink 2001;41:503—6.

[10] Zaja F, Barillari G, Russo D, Silvestri F, Fanin R, Baccarani M. Myasthenia gravis after allogeneic bone marrow transplantation: a case report. Bone Marrow Transpl 1995;15:649—50.

[11] Adams C, August CS, Maguire H, Slady JT. Neuromuscular complications of bone marrow transplantation. Pediat Neurol 1995;12:58—61.

[12] Shimoda K, Gondo H, Harada M, Sano T, Nakamura M, Otsuka T, et al. Myasthenia gravis after allogeneic bone marrow transplantation. Bone Marrow Transpl 1994;14:155—6.

[13] Haslam PJ, Proctor SJ, Goodship TH, Zouvani J. Immune complex glomerunephritis, myasthenia gravis and compensated hypothyroidism in a patient following allogeneic bone marrow transplantation. Nephrol Dial Transpl 1993;8:1390—2.

[14] Melms A, Faul C, Sommer N, Wietholter H, Muller CA, Ehninger G. Myasthenia gravis after BMT: identification of patients at risk? Bone Marrow Transpl 1992;9:78—9.

[15] Abecassis MM. Complicacoes pouco habituais da transplantacao de medulla ossea (TMO). Experiencia da Unidade de TMO do Instituo Portugus de Oncologia de Francisco Gentil, Centro de Lisboa. Acta Med Portuguesa 1991;4:37—8 [in Portuguese].

[16] Grau JM, Casademont J, Monforte R, Marin P, Granena A, Rozman C, et al. Myasthenia gravis after allogeneic bone marrow transplantation: report of a new case and pathogenetic considerations. Bone Marrow Transpl 1990;5:435—7.

[17] Atkinson K, Bryant D, Delprado W, Biggs J. Widespread pulmonary fibrosis as a major clinical manifestation of chronic graft-versus-host disease. Bone Marrow Transpl 1989;4:129—32.

[18] Lefvert AK, Bjorkholm M. Antibodies against the acetylcholine receptor in hematologic disorders: implications for the development of myasthenia gravis after bone marrow grafting. N Engl J Med 1987;317:170.

[19] Bolger GB, Sullivan KM, Spence AM, Appelbaum FR, Johnston R, Sanders JE, et al. Myasthenia gravis after allogeneic bone marrow transplantation: relationship to chronic graft-versus-host disease. Neurology 1986;36:1087—91.
[20] Seely E, Drachman D, Smith BR, Antin JH, Ginsburg D, Rappaport JM. Post bone marrow transplantation (BMT) myasthenia gravis: evidence for acetylcholine receptor (AChR) abnormality. Abstract. Blood 1984;64:221a.
[21] Unal S, Sag E, Kuskonmaz B, Kesici S, Bayrakci B, Ayvaz DC, et al. Successful treatment of severe myasthenia gravis developed after allogeneic hematopoietic stem cell transplantation with plasma exchange and rituximab. Pediatr Blood Cancer 2014;61:928—30.
[22] Heidarzadeh Z, Mousavi SA, Ostovan VR, Nafissi S. Muscle-specific kinase antibody associated myasthenia gravis after bone marrow transplantation. Neuromuscul Disord 2014;24:148—50.
[23] Meriggioli MN, Sanders DB. Autoimmune myasthenia gravis: emerging clinical and biological heterogeneity. Lancet Neurol 2009;8:475—90.
[24] Smith CI, Norberg R, Moller G, Lonnqvist B, Hammarstrom L. Auto antibody formation after bone marrow transplantation. Comparison between acetylcholine receptor antibodies and other autoantibodies and analysis of HLA and Gm markers. Eur Neurol 1989;29:128—34.
[25] Teshima T, Wynn TA, Soiffer RJ, Matsuoka K, Martin PJ. Chronic graft-versus-host disease: how can we release Prometheus? Biol Blood Marrow Transpl 2008;14:142—50.
[26] Mikos DB, Kim HT, Zorn E, Hochberg EP, Guo L, Mattes-Ritz A, et al. Antibody response to DBY minor histocompatibility antigen is induced after allogeneic stem cell transplantation and in healthy female donors. Blood 2004;103:353—9.
[27] Mikos DB, Kim HT, Miller HT, Guo L, Zom E, Lee SJ, et al. Antibody responses to H-Y minor histocompatibility antigens correlate with chronic graft-versus-host disease and disease remission. Blood 2005;105:2973—8.
[28] Zorn E, Miklos DB, Floyd BH, Mattes-Ritz A, Guo L, Soiffer RJ, et al. Minor histocompatibility antigen DBY elicits a coordinated B and T cell response after allogeneic stem cell transplantation. J Exp Med 2004;199:1133—42.
[29] Grauer O, Wolff D, Bertz H, Greinix H, Kuhl JS, Lawitschka A, et al. Neurological manifestation of chronic graft-versus-host disease after allogeneic haematopoietic stem cell transplantation: report from the consensus conference on clinical practice in chronic graft-versus-host disease. Brain 2010;133:2852—65.