Clin. Lab. 2021;67:XXX-XXX

CASE REPORT

Role of Therapeutic Plasma Exchange in Guillain-Barre Syndrome after Allogeneic Hematopoietic Stem Cell Transplant: Report of Two Cases

Demet Cekdemir [1], Hasan A. Ozkan [1], Ferda Korkmaz [2], Yesim Ozgurel [1], Serap Kural [1], Neslihan Tiryaki [1], Zafer Gulbas [1]

[1] *Department of Bone Marrow Transplantation, Anadolu Medical Center, Gebze, Kocaeli, Turkey*
[2] *Department of Neurology, Anadolu Medical Center, Gebze, Kocaeli, Turkey*

SUMMARY

Background: **Guillain-Barre Syndrome (GBS) is an acute inflammatory polyneuropathy characterized with rapid, progressive, ascending, and symmetrical weakness and areflexia. It is supposed to be an autoimmune disease related with production of antibodies by T lymphocytes activated against antigenic proteins of the peripheral nerves. Guillain-Barre Syndrome occurring after hematopoietic stem cell transplant (HSCT) has been associated with viral infections or toxic effects of chemotherapy.**
Methods: **We report two GBS cases after HSCT treated successfully by means of therapeutic plasma exchange.**
Results: **In a total of 257 patients, 2 cases (0.8%) were diagnosed with GBS following HSCT. Allogeneic HSCT was performed and complete remission was achieved. Diagnosis of GBS was established on the 45th and 69th days with respect to clinical, cerebrospinal fluid, and electromyography findings. Patients did not respond to treatment consisting of intravenous immunoglobulins (IVIG) (1 g/kg/day) for 2 days and methylprednisolone (1 mg/kg/day). Mechanical ventilation was indicated in one patient due to the involvement of respiratory muscles. Therapeutic plasma exchange resulted in complete recovery in both cases.**
Conclusions: **Guillain-Barre Syndrome is a rare but serious complication, which may occur after HSCT. Increased awareness and early diagnosis are crucial in the management of GBS. First line treatment consists of IVIG and steroids and therapeutic plasma exchange must be considered without delay in refractory cases.**
(Clin. Lab. 2021;67:xx-xx. DOI: 10.7754/Clin.Lab.2020.200613)

Correspondence:
Prof. Dr. Zafer Gulbas, MD
Department of Hematology
Bone Marrow Transplantation Center
Anadolu Medical Center
Gebze, Kocaeli
Turkey
Phone: +90 5323342726
Fax**:** +90 2626785545
Email: zafer.gulbas@anadolusaglik.org

Case Report accepted October 18, 2020

KEY WORDS

Guillain-Barre Syndrome, hematopoietic stem cell transplantation, treatment, plasma exchange

INTRODUCTION

Guillain-Barre Syndrome (GBS) is the most frequent form of acute generalized paralysis [1]. It is characterized by weakness in the limbs, loss of deep tendon reflexes, absent or mild sensory deficits, and variable autonomic dysfunction [2]. Even though the underlying pathophysiological mechanism has not been clearly elucidated yet, aberrant immunological mechanisms have been linked with GBS [2]. In the majority of cases, the neuropathy is precipitated by a bacterial (e.g., *Campylo-*

bacter jejuni) or viral (e.g., *cytomegalovirus*) infection [3,4]. Primary T-lymphocytic responses are supposed to lead to the inflammation and polyneuropathy by affecting the myelin sheath of peripheral nerves [4].

Mortality has been observed in 4.5% of GBS patients, and nearly 30% of patients need mechanical ventilation [5]. Hematopoietic stem cell transplant (HSCT) recipients are under risk for neurologic complications. These adverse events may result either from the primary disease for which the patient underwent HSCT, from the infection that occurs during HSCT, or as a result of other treatment [5]. Guillain-Barre Syndrome is an uncommon manifestation of neurotoxicity during HSCT and has usually been attributed to infection [6].

As a rare complication after allo-HSCT, common modes of treatment for GBS include intravenous immunoglobulins (IVIG) and plasma exchange [5,7]. Owing to the primary malignancy, low immunity after transplantation, infection, graft-versus-host disease and other morbidities; the prognosis can be worsened and rate of mortality may be increased [8].

In this report, we present two GBS cases that developed late after allo-HSCT. These patients did not initially respond to steroid and IVIG treatment, but complete recovery was accomplished with therapeutic plasma exchange.

CASE REPORTS

Case 1

A 17-year-old white woman diagnosed with acute myelogenous leukemia received allo-HSCT after a conditioning regimen consisting of busulfan and cyclophosphamide. Febrile neutopenia was accepted as a fever of unknown origin after transplantation. Grade II graft-versus-host disease affecting primarily the skin was controlled with steroid treatment. Engraftment occured within the expected period and complete remission was confirmed with cytologic analysis of bone marrow and flow cytometry. Chimerism test on the 28th day was 100% compatible with the donor. Prior to discharge, the patient was admitted with paresthesias of the limbs and ascending weakness on the 45th day after HSCT. Cranial magnetic resonance imaging was normal. No findings consistent with viral or bacterial infection were observed. Diagnosis of GBS was established with respect to clinical data, nerve conduction studies, and increased protein amount in the cerebrospinal fluid. No response was observed to IVIG and steroid treatment. Plasma exchange was conducted and complete recovery was achieved after 10 courses.

Case 2

A 47-year-old Caucasian man diagnosed with acute myelogenous leukemia transformed from myelodysplastic syndrome received allo-HSCT. Conditioning before transplant was done with fludarabine and busulfan. After an uneventful follow-up period, the patient admitted with an acute polyneuropathy on the 69th day after HSCT. Normal cranial imaging was accompanied with increased cerebrospinal fluid protein. Viral or bacterial infection and graft-versus-host disease were excluded and treatment for GBS including IVIG and steroid was started. Not only was no therapeutic response observed, but also respiratory failure necessitating mechanical ventilation developed. Plasma exchange and thioctacid was administered and the patient exhibited excellent functional and clinical recovery as reflected in electromyographic findings.

DISCUSSION

Guillain-Barre syndrome is a complex autoimmune disorder with many vague points on pathogenesis. In this report, both patients were immunosuppressed and when conditioning regimen prior to HSCT was reviewed, it could be postulated that cellular immunity was obviously more suppressed. Similar tendencies were reported in relevant publications [2,9,10]. Male patients are reported to be more likely to be affected by GBS; however, our data is insufficient to make a conclusion [2]. In accordance with literature, the onset of GBS was within three months after the transplant [2]. Our findings do not support the role of bacterial or viral infection in the pathogenesis of GBS. Even though IVIG treatment has been recommended in GBS, we did not have any favorable response in both of our patients. However, complete clinical and functional recovery was observed after initiation of plasma exchange. Therefore, we suggest that critical review of treatment of GBS in patients that received HSCT must be made and plasma exchange must be considered as a promising alternative in these cases. Since respiratory failure and need for mechanical ventilation may arise, treatment plan should be made without delay. Vembu et al. reported that in spite of the severity of weakness, a good therapeutic response can be obtained with IVIG instead of plasma exchange, a more invasive approach [11]. However, their experience was derived from a patient with acute lymphoblastic leukemia receiving chemotherapy. The treatment plan must be made on an individualized basis for patients who underwent transplantation [11]. From this point of view, our findings are controversial to the report by Fujika et al. [12]. They suggested that IVIG should be preferred as the mode of treatment and there was little evidence for the usefulness of plasma exchange for GBS after HSCT [12]. Our data is in alignment with Bulsara et al. who suggested that plasma exchange was emerging as the preferential modality of treatment in transplant patients where it is difficult to establish a definitive pathological mechanism [2].

Interestingly, resolution of GBS in patients with a history of allo-HSCT was associated with the return of T-cell function [9,10]. In contrast, Bulsara et al. suggested that patients with defects of T-cell function exhibited a course of recovery similar to those of transplant patients

with partial supression of T-cell functions [2]. The immunological basis of GBS must be studied in molecular and clinical trials to elucidate the underlying pathophysiological mechanism.

Not only cellular immunity, but also humoral mechanisms may be involved in GBS. Experimental studies provided evidence for the humoral inflammatory demyelination induced by intraneural injection of galactocerebroside or anticerebroside antibody [13]. Our HSCT patients displayed excellent functional recovery in spite of the continuity of their T-cell mediated immunosuppression [2]. Bulsara et al. suggested that T-lymphocytes are not always necessary for the supression of the auto-immune response [2]. Thus, the role of the whole immune system and effects of the humoral immune response must not be overlooked in the pathophysiology of GBS in transplant patients [10].

As has previously been reported, our bone marrow transplant patients made excellent functional recovery [2,10,12]. Whether GBS occurs as a consequence of neurotoxic effects of the conditioning regimen is under debate. Cumulative doses of cytosine arabinoside (Ara-C) has been associated with GBS and cessation of it for patients with leukemia has been recommended [5]. One of our patients had received fludarabine for this purpose, and we agree that other alternatives should be preferred in the conditioning regimen prior to HSCT. Other factors likely to contribute to the neurotoxicity involve cranial irradiation and administration of high dose methotrexate [5]. Our patients were devoid of the possible hazardous effects of these agents. However, careful assessment of patient history and increased awareness on the complications of chemotherapy as well as selection of safer therapeutic options are important to avoid GBS in candidates of HSCT.

In spite of treatment, rates of need for mechanical ventilation, mortality, and disability in GBS patients are 25%, 15%, and 20%, respectively [14]. The prognosis of patients who had GBS following allo-HSCT is especially poor and mortality rates as high as 34% has been reported. Treatment targets the pathogenic antibodies developed against peripheral nerve tissues, either by means of IVIG or plasma exchange [14]. An infection has been detected in two-thirds of patients before the diagnosis of GBS [15].

Complete recovery has been observed in patients diagnosed with GBS after vincristine treatment for acute lymphoblastic leukemia improving within a few weeks with IVIG treatment [11,14]. Simultaneously, substantial mortality has also been reported due to GBS after HSCT in recent publications [5,8,15]. Rituximab is a monoclonal antibody that targets CD20 that has been successfully used for chronic neuropathy [15]. As a novel and promising therapeutic agent, rituximab has been used to treat GBS after allo-HSCT [15].

Our data indicate that GBS can occur as a serious condition after allo-HSCT. Since deterioration of the clinical picture may necessitate mechanical ventilation and risk for mortality, early diagnosis and initiation of appropriate treatment without delay are crucial. Plasma exchange can be a life saving alternative in selected cases who do not respond to supportive treatment and IVIG.

Acknowledgment:
None.

Financial Support:
No financial support was received for this paper.

Declaration of Interest:
The authors declare no competing interest.

References:

1. Ropper AH. The Guillain-Barré syndrome. N Engl J Med 1992; 326:1130-6 (PMID: 1552914).
2. Bulsara KR, Baron PW, Tuttle-Newhall JE, Clavien PA, Morgenlander J. Guillain-Barre syndrome in organ and bone marrow transplant patients. Transplantation 2001;71:1169-72 (PMID: 11374420).
3. Kaldor J, Speed BR. Guillain-Barré syndrome and Campylobacter jejuni: a serological study. Br Med J (Clin Res Ed) 1984;288: 1867-70 (PMID: 6428580).
4. Koski CL, Chou DK, Jungalwala FB. Anti-peripheral nerve myelin antibodies in Guillain-Barre syndrome bind a neutral glycolipid of peripheral myelin and cross-react with Forssman antigen. J Clin Invest 1989;84:280-7 (PMID: 2738153).
5. Rodriguez V, Kuehnle I, Heslop HE, Khan S, Krance RA. Guillain-Barré syndrome after allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant 2002;29:515-7 (PMID: 11960272).
6. Hahn AF. Guillain-Barré syndrome. Lancet 1998;352:635-41 (PMID: 9746040).
7. Rumpl E, Mayr U, Gerstenbrand F, Hackl JM, Rosmanith P, Aichner F. Treatment of Guillain-Barre syndrome by plasma exchange. J Neurol 1981;225:207-17 (PMID: 6167686).
8. Xu X, Jia L, Chen L, Zhang W, Wang J. [Guillain-Barre syndrome after allogeneic hematopoietic stem cell transplantation: two cases report and literature review]. Zhonghua Xue Ye Xue Za Zhi 2014;35:694-7 (PMID: 25152114).
9. Baldwin RT, Pierce RR, Frazier OH. Guillain-Barré syndrome after heart transplantation. J Heart Lung Transplant. 1992;11:817-9 (PMID: 1323331).
10. Qureshi AI, Cook AA, Mishu HP, Krendel DA. Guillain-Barré syndrome in immunocompromised patients: a report of three patients and review of the literature. Muscle Nerve 1997;20:1002-7 (PMID: 9236791).
11. Vembu P, Al-Shubaili A, Al-Khuraibet A, Kreze O, Pandita R. Guillain-Barré syndrome in a case of acute lymphoblastic leukaemia. A case report. Med Princ Pract 2003;12:272-5 (PMID: 1296 6204).

12. Fujisaki G, Kami M, Murashige N, et al. Guillain-Barre syndrome associated with rapid immune reconstitution following allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant 2006;37:617-9 (PMID: 16444281).

13. Saida T, Saida K, Dorfman SH, et al. Experimental allergic neuritis induced by sensitization with galactocerebroside. Science 1979;204:1103-6 (PMID: 451555).

14. Amato AA, Barohn RJ, Sahenk Z, Tutschka PJ, Mendell JR. Polyneuropathy complicating bone marrow and solid organ transplantation. Neurology 1993;43:1513-8 (PMID: 8394521).

15. Ostronoff F, Perales MA, Stubblefield MD, Hsu KC. Rituximab-responsive Guillain-Barré syndrome following allogeneic hematopoietic SCT. Bone Marrow Transplant 2008;42:71-2 (PMID: 18 391992).