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BRIEF REPORT
Successful Treatment of Severe Myasthenia Gravis Developed After Allogeneic Hematopoietic Stem Cell Transplantation With Plasma Exchange and Rituximab

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Myasthenia gravis is among the rare complications after allogeneic hematopoietic stem cell transplantation and is usually associated with chronic GVHD. Herein, we report a 2-year and 10 months of age female with Griscelli syndrome, who developed severe myasthenia gravis at post-transplant +22nd month and required respiratory support with mechanical ventilation. She was unresponsive to cyclosporine A, methylprednisolone, intravenous immunoglobulin, and mycophenolate mofetil and the symptoms could only be controlled after plasma exchange and subsequent use of rituximab, in addition to cyclosporine A and mycophenolate mofetil maintenance. She is currently asymptomatic on the 6th month of follow-up. Pediatr Blood Cancer 2014;61:928–930.

Key words: bone marrow transplantation; graft-versus-host disease; Griscelli syndrome; myasthenia gravis; plasma exchange; rituximab

INTRODUCTION

Myasthenia gravis (MG) is an antibody-mediated autoimmune disease and has been reported as a rare complication of chronic graft-versus-host disease (GVHD) after allogeneic hematopoietic stem cell transplantation (HSCT) [1]. The latency period of MG after allogeneic HSCT is 22–60 months [2] and usually develops during the tapering of immunosuppressive treatments. Myasthenic symptoms are frequently associated with other symptoms of chronic GVHD [3,4]. However, there are few reports describing development of MG in the absence of chronic GVHD symptoms [5].

The data on the treatment of MG seen during the post-HSCT period are limited. The present case developed MG after HSCT associated with chronic GVHD.

CASE REPORT

A 1-month old female presented with fever and silvery gray hair was diagnosed to have Griscelli syndrome. At 6 months of age, she developed accelerated phase of the disease and HLH-2004 protocol was initiated [6]. Bone marrow transplantation was performed from HLA-1 antigen mismatched grandmother at 1 year of age. The conditioning regimen included busulfan (i.v., 4 mg/kg/day on −10th, −9th, −8th, −7th days), cyclophosphamide (i.v., 50 mg/kg/day, on −5th, −4th, −3rd, −2nd days), etoposide (i.v., 300 mg/m^2/day on −5th, −4th, −3rd days).GVHD prophylactic regimen consisted of cyclosporine A (CyA) plus methotrexate. Neutrophil and platelet engraftments were observed on the 10th and 14th days, respectively. On day +8, she developed diarrhea and methylprednisolone was initiated for engraftment-associated inflammatory state. Diarrhea remitted and steroid was tapered and ceased on +36th day. During the dose decrement of CyA, at +6th month, the patient developed elevated liver enzymes and generalized maculopapular rash. Methylprednisolone was re-initiated and CyA was increased with a diagnosis of chronic GVHD supported by skin biopsy.

On the post-transplant 22nd month, at 34 months of age, while methylprednisolone (2 mg/day) and CyA was being tapered, she presented with ptosis on the left eye and slight hoarseness. Hemogram, serum biochemistry, cerebrospinal fluid investigations for culture, HSV, CMV, and toxoplasma infections and cranial imaging with contrast were not indicative of any pathology including central nervous system infections and cerebral involvement of hemophagocytic lymphohisticytosis. Anti-nuclear antibody testing revealed positivity at 1/100 titer. Toxicity of CyA was suspected and CyA was stopped. She developed severe dyspnea and required mechanical ventilation. Cyclosporine A was re-initiated and extubation was successful on the 5th day. Fifteen days later, she again presented with fatigue, difficulty in speech, bilateral ptosis, and dyspnea, and required respiratory support with mechanical ventilation for 5 more days and was then extubated. The ocular and bulbar findings, perpetuated with recurrent respiratory crises prompted a diagnosis of MG associated with chronic GVHD. Serum acetylcholine receptor antibody (AChR-Ab) level was found 56 nmol/L (normal: <0.4 nmol/L). Cyclosporine A was substituted with mycophenolate mofetil (MMF; 30 mg/kg/day). Intravenous immunoglobulin (IVIG) (400 mg/kg/day, 5 days) and methylprednisolone (2 mg/day) were initiated. Pyridostigmine (3 mg/kg/day) was added and tapering of steroids was initiated. Ptosis and other symptoms disappeared. During an upper respiratory tract infection, myasthenic symptoms aggrevated. Pyridostigmine was gradually increased to 6 mg/kg/day, prednisolone to 2 mg/kg/day and a second course of IVIG was given. At the second day of IVIG, respiratory insufficiency developed and she was admitted to ICU for non-invasive mechanical ventilation. The serum AChR-Ab level at this

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time was measured as 37 nmol/L. Bolus methylprednisolone (30 mg/kg/day, 3 days), in addition to i.v. CyA were initiated and plasma exchange (PE) was done in order to remove the AChR-Ab's every other day, for five times with one volume exchange. The serum AChR-Ab level after the 1st PE was 17 nmol/L. After the 1st PE, she became free of ventilation support for 8 hours. After the 2nd PE, she did not require ventilation support. After completion of the 5 days of PE, serum AChR-Ab level dropped to 14 nmol/L (Fig. 1). Steroid dose was tapered off and discontinued followed by rituximab (i.v., 375 mg/m^2/week, for 4 weeks). The lymphocyte subset at last visit from peripheral blood revealed CD3: 76%, CD19: 7%, CD4/CD8 = 1.4. Currently, the patient is asymptomatic, with 99% donor chimerism, on the 6th month of follow-up after MG development, under oral CyA, MMF, pyridostigmine. Monthly IVIG and co-trimoxazole were given for infection prophylaxis.

DISCUSSION

GVHD is the leading cause of morbidity and mortality after allogeneic HSCT, affecting multiple organs. The pathophysiological factors in chronic GVHD development are thymic destruction by alloreactive T cells, a T helper 1 to T helper 2 shift of the cellular immune response, replacement of antigen presenting cells of the host by antigen presenting cells of the donor leading to indirect antigen presentation of allo-antigens and donor-derived B cells producing antibodies against the host [1,7,8]. B cells seem to have a more prominent role compared to acute GVHD and high prevalence of the autoimmune antibodies may support the role of B lymphocytes in this complication [9,10]. This is supported by the appearance of AchR-Ab's during the tapering of immunosuppressive treatment.

Among the neurological manifestations of chronic GVHD are myositis, Guillain Barre Syndrome, MG, demyelinating diseases and encephalitis [1]. MG is an autoimmune disorder mediated via most commonly AChR-Ab or to a lesser extent muscle specific tyrosine kinase antibodies [7]. Although, asymptomatic development of AChR-Ab are common almost half of these patients do not develop MG [11,12].

The myasthenic symptoms were absent when initial diagnosis of chronic GVHD was made at +6th month, however developed while immunosuppressive drug doses were being decreased at +22nd month. At the initial presentation with unilateral ptosis, the diagnosis of MG was not suspected and the symptoms were attributed to CyA toxicity. It has been previously reported 3 patients among 582 allogeneic HSCT who developed ptosis secondary to CyA use in combination with ganciclovir and recovered after discontinuation of both drugs [13]. However, our patient required mechanical ventilation after cessation of CyA. The electromyography was not ordered because of the age of the patient. Serum AChR-Ab was positive in high titer. Previously reported pediatric patients with this presentation were 4, 6, 9, 9, 12 years of age [14–16]. Our patient did not have myasthenic symptoms prior to HSCT and AChR-Ab was found to be positive, excluding congenital MG. The donor was investigated for MG after the clinical picture developed in our case and was negative for myasthenia.

The treatment options for MG include prednisolone, CyA, tacrolimus, MMF, IVIG, and cyclophosphamide [1]. However, in refractory or severe MG, PE may be life-saving [17]. Some

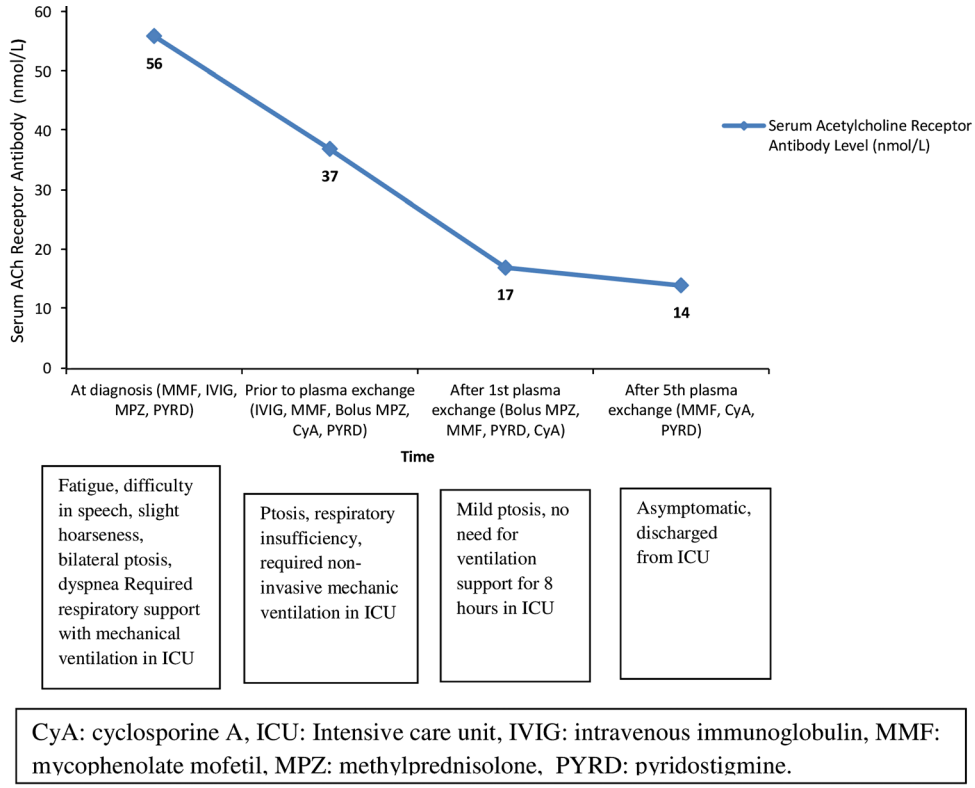

Fig. 1. Serum acetylcholine receptor antibody level, the associated symptoms at the time of measurement and the treatment.

refractory cases have been reported to benefit from rituximab [18]. Our patient could only respond to PE and rituximab and the treatment was maintained by CyA and MMF. The anti-CD20 chimeric monoclonal antibody rituximab has been reported to be beneficial in one case of a refractory chronic GVHD patient with MG, previously [19].

Although, there are reports that change in serum AChR-Ab levels do not predict the severity of the MG [20], the sharp decline in our patient after PE was in correlation with the clinical improvement (Fig. 1). Plasma exchange may be used in refractory cases with life-threatening symptoms including respiratory difficulties and bulbar symptoms in order to decrease ICU admissions. The data on the management of chronic GVHD associated MG are limited and successful sustained response with PE and rituximab in our patient may be promising for the refractory cases.

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