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Case report

Autologous hematopoietic stem cell transplantation in a patient with refractory seropositive myasthenia gravis: A case report

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Abstract

Myasthenia gravis is a neuromuscular autoimmune disease characterized by fatigable weakness of skeletal muscles that results from an antibody-mediated immunological attack directed at acetylcholine postsynaptic receptors. Autologous hematopoietic stem cell transplantation is considered as a treatment option in refractory cases of myasthenia gravis. A 56-year-old Colombian male presented with six months of progressive hoarseness and dysphagia, with a positive repetitive stimulation test suggestive of end plate neuromuscular disease. Myasthenia gravis was confirmed with serology testing that reported presence of circulating acetylcholine postsynaptic receptors antibodies. The patient received several lines of pharmacological treatment and thymectomy without control of symptoms, requiring admission to the intensive care unit and mechanical ventilation in two occasions. Patient underwent autologous hematopoietic stem cell transplantation and has been in complete clinical remission for 65 months. Hematopoietic stem cell transplantation is a well-tolerated treatment that should be considered over conventional therapy in selected patients with refractory myasthenia gravis.

Keywords: Miastenia gravis; Refractory; Autologous hematopoietic stem cell transplantation; Treatment.

1. Introduction

Myasthenia gravis (MG) is a neuromuscular autoimmune disorder caused by an antibody-mediated, T-cell dependent immunologic attack directed at proteins in the postsynaptic membrane of the neuromuscular junction (acetylcholine receptors or receptor-associated proteins) [1]. While the prevalence of this disorder is unknown in Colombia, this condition affects 20 people per 100,000 inhabitants in the United States. MG has a bimodal age of onset with a peak of incidence occurring between 20 and 30 years of age in women, and a second peak between 60 and 70 years of age in both women and men [1]. There is no evidence of a hereditary component in MG, but it is associated with other autoimmune diseases like autoimmune thyroid disease, rheumatoid arthritis, and systemic lupus erythematosus [2]. Diagnosis can be established with history and clinical examination and confirmed with serological testing. Immunological assay to detect presence of circulating acetylcholine receptor antibodies (AChR-Ab) confirms seropositive MG, the most frequent type of MG representing 85% of the cases. Antibodies to MuSK (muscle specific receptor tyrosine kinase) are present in 38 to 50 percent of those with generalized myasthenia gravis who are AChR-Ab negative [3].

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The first therapeutic approach to MG is focused on symptomatic treatment with acetylcholinesterase inhibitors, which increase the amount of acetylcholine at neuromuscular endplates after motor nerve stimulation improving muscle weakness; pyridostigmine is the preferred drug from this group [4]. More severe cases require rapid immunomodulating treatments with plasmapheresis or intravenous immunoglobulin, followed by chronic immunomodulating treatments with glucocorticoids and other immunosuppressive drugs as azathioprine, methotrexate, cyclosphosphamide, mycophenolate or cyclosporine. Thymectomy is the treatment choice in cases of thymoma. Despite treatment, a proportion of myasthenia gravis patients are classified as refractory due to non-responsiveness to conventional treatment [5]. Alternative immunotherapies such as rituximab are available for these patients; however, the efficacy of this treatment continues being a field of ongoing research [6]. Autologous hematopoietic stem cell transplantation (HSCT) has been used since 1996 in the treatment of severe autoimmune diseases refractory to conventional therapy [7]. Autologous HSCT is considered a therapeutic option in the following cases: 1) patients with severe disease, high disability, and/or high risk of death; 2) patients who have no response to conventional treatments; and 3) patients without permanent organ damage [8]. Nevertheless, reports in literature of autologous transplantation in MG patients are very limited.

To our knowledge, there are no reports of autologous HSCT in patients with refractory MG (RMG) in Colombia, South America. The aim of this case report is to present the experience of a patient with seropositive RMG that underwent autologous HSCT at a tertiary referral center.

2. Case report

A 56-year-old male presented to the neurology clinic in April 2008 with complains of progressive dysphonia and dysphagia for the past six months that evolved to inability to swallow. Patient had no significant medical history. Complete blood work was normal. Repetitive stimulation test was positive for neuromuscular plate disease, circulating AChR-Ab were detected by immunoassay while anti-MUSK antibodies were negative, thus confirming seropositive MG. Initial pharmacological therapy consisted of azathioprine, pyridostigmine, and prednisone. Despite administered treatment his symptoms persisted. In December 2008, after completing a cycle of intravenous immunoglobulin, total thymectomy was performed. Symptoms reappeared in September 2009 and azathioprine was switched to cyclosporine, which caused renal failure and azotemia. Cyclosporine was suspended and mycophenolate mofetil was initiated instead. The patient continued presenting symptoms and the frequency of myasthenic crises increased. In April 2010, the patient developed respiratory failure and plasmapheresis was started with remission of symptoms. One year later, the patient presented a new episode of severe dysphagia and quadriparesis, managed unsuccessfully with intravenous immunoglobulin. A plasmapheresis cycle was administered with temporary recovery and early relapse. Treatment was continued with Rituximab for two months with no satisfactory response. The patient required monthly plasmapheresis and chronic immunomodulating treatment with mycophenolate, prednisone, and azathioprine to maintain basic functionality; however, severe dysphagia, dysarthria, and bilateral ptosis persisted.

In July 2012, the hospital's Hematology and Neurology Medical Board reviewed the case and agreed on performing an autologous HSCT, considering this was the best option for the patient. Mobilization of hematopoietic progenitor cells was done using cyclophosphamide at a dose of 7.6 g (2 g/m^2) and granulocyte colony-stimulating factor at a dose of 10 μg/kg/day for 5 days. A total of 7×10^6/kg CD34 hematopoietic stem cells were collected. Pre-transplant conditioning regimen included cyclophosphamide at 50 mg/kg/day for 4 days with anti-thymocyte globulin at 2.5 mg/kg/day for 3 days. A total dose of 7×10^6 per kg CD34-positive cells were infused. Engraftment was defined as absolute neutrophil count of $> 0.5 \times 10^9$/L and platelet count of $> 20 \times 10^9$/L on the 10th day post-HSCT. The patient presented fever on day +8, but no bacteremia or fungal infections were evidenced in blood cultures. Antibiotic treatment with meropenem plus vancomycin was started, and tigecycline and caspofungin were administered until fungaemia was ruled out. On day +22, cytomegalovirus reactivation was confirmed by polymerase chain reaction (PCR) amplification and was managed with valganciclovir until a negative viral load was reached. The patient was discharged from the hospital on day +23. Treatment with pyridostigmine was suspended on day +60 post-transplantation, and corticosteroids were weaned until complete withdrawal on day +120. Sixty-five months after autologous HSCT the patient remains in complete remission.

3. Discussion

RMG is characterized by lack of clinical response, frequent relapses, and impossibility to reach complete remission of the disease. RMG represents only a small percentage of the total patients with MG. In a retrospective study conducted by Nowak et al on 128 patients diagnosed with MG in the United States, 15% were identified as refractory MG [5]. The population of this study showed an earlier age of onset of the disease in the refractory group when comparing it with the non-refractory group, as well as a significantly higher proportion of female refractory patients. The study also found a significantly higher proportion of refractory patients presenting anti-MuSK antibodies compared to non-refractory patients, concluding that MuSK-antibody positive MG patients would be more likely to have refractory disease. Contrary to the data reported by the Nowak et al study, our patient presented a late onset of the disease (>50 years old), was found to have circulating Anti-AchR antibodies, and underwent early thymectomy, with recurrence of refractory symptoms despite aggressive immunosuppressive treatment.

Symptomatic treatment with drugs that increase the amount of acetylcholine at neuromuscular endplates after motor nerve stimulation to improve the neuromuscular transmission is the

first line treatment in patients with MG [6]. Patients who do not respond to symptomatic therapy alone require adding immunosuppressive drug treatment. Studies comparing alternative immunosuppressive treatments in patients with MG are uncommon and difficult to find. Therefore, recommendations on the best immunosuppressive therapy approach for MG are made based on several retrospective studies with weak evidence and guidelines, clinical experience, and consensus reports [8]. Treatment effect and adverse effects are dose dependent, thus each patient should be approached individually when selecting the best dosage. Azathioprine remains the first-choice for long-term immunosuppressive therapy and is usually started in combination with prednisolone to achieve a rapid therapeutic effect [9].

Second-line immunosuppressive medications are initiated in non-responsive patients to treatment with azathioprine and glucocorticosteroids. Cyclosporine selectively inhibits calcineurin, thereby impairing the transcription of interleukin-2 (IL-2) and several other cytokines in T lymphocytes. The efficacy of cyclosporine was assessed in a double-blind and placebo-controlled trial by Tindall et al in 1993, concluding that cyclosporine is an effective immunosuppressant managing the symptoms of myasthenia [10]. Patients in the cyclosporine group had significantly greater improvement in strength and reduction in antibody titers than those in the placebo group. A European study comparing low-dosage cyclosporine to azathioprine found both drugs equally efficacious improving symptoms in myasthenic patients [11]. However, due to limited evidence on the use of cyclosporine, numerous drug interactions, and serious cumulative side effects such as nephrotoxicity, cyclosporine remains as a reserve treatment for refractory patients.

Another immunosuppressant administered for RMG is mycophenolate mofetil (MMF), a powerful inhibitor of lymphocyte proliferation. MMF reversibly inhibits inosine monophosphate dehydrogenase in purine synthesis, depleting guanine nucleotides and thereby inhibiting DNA synthesis in lymphocytes. Several retrospective case-series studies have shown this therapy to be highly beneficial [9]. It has been demonstrated that MMF, as monotherapy or combined with glucocorticosteroids, begins to improve AChR-positive MG after 6 months of treatment [12,13].

Despite the different therapies mentioned above, there are patients who persist refractory. Emerging therapies using monoclonal antibodies have been a promising alternative in the treatment of MG. Rituximab is a genetically engineered chimeric murine/human monoclonal antibody. It binds specifically to the transmembrane antigen CD20, a non-glycosylated phosphoprotein located in pre-B and mature B lymphocytes. B cell depletion begins within 6 months of treatment and returns to normal levels after 9–12 months [9,14]. Studies on the efficacy and safety of rituximab in patients with RMG showed a significant response to treatment, their reports suggest that it can be helpful managing the disease [15–17]. A prospective study with long-term follow-up by Anderson et al 2016, examined the clinical effectiveness of rituximab in patients with RMG. All patients responded dramatically to rituximab as measured by a change in manual muscle testing (MMT) score, prednisone dose, or the frequency of IV immunoglobulin infusions or plasma exchange (PLEX) [18]. Rituximab is a drug that appears to be safe and effective and should be considered as a treatment option in patients with non-responsive MG. Furthermore, a study by Diaz-Manera et al. analyzing the long-term response of Rituximab in RMG patients demonstrated that Rituximab induces a long-lasting clinical benefit in severely affected non-responsive MG [19].

More than two decades ago, experts in the field of stem cell transplantation and autoimmune diseases explored the possibility of performing HSCT, a procedure previously reserved for hematologic and oncologic disorders, to treat severe autoimmune diseases [20]. Since then, more than 1800 HSCT have been performed to manage patients with severe autoimmune diseases [21]. Data obtained from retrospective studies by the European Group for Blood and Marrow Transplantation (EBMT) and the European League Against Rheumatism (EULAR) suggest that high-dose chemotherapy followed by autologous HSCT could manage or even cure patients with autoimmune diseases by inducing fundamental immunologic changes that have not been observed with other therapies [9]. These immunological changes include normalization of restricted T cells, with sustained changes in the B and T cells subpopulations from memory to predominantly new and naive populations reconstituted from the stem cell graft, which will re-establish immune tolerance through the thymus [8,21,22]. Additionally, a normalization of CD4 regulatory cells is observed, with disappearance of the plasmablasts [23].

An observational study on autologous HSCT in 900 patients with serious and refractory autoimmune diseases over a 12-year period demonstrated that autologous HSCT can induce sustained remission for more than 5 years in patients with severe autoimmune diseases non-responsive to conventional treatment [7]. Despite the small number of patients with MG included in the study, results were favorable for this group [7]. Survival rate at 5 years post-transplantation was 85%, and mortality rate at 100 days post-HSTC was lower in centers with greater transplant experience, varying according to the autoimmune disease. Håkansson et al also reported a case of a 64 year old woman with severe RMG successfully treated with autologous HSCT [24]. Additionally, Bryant et al published a case series in 2016 describing seven patients with severe RMG who underwent autologous HSCT followed by a prolonged and complete symptom-free and treatment-free remission [25]. Autologous HSTC continues to be the preferred choice over allogeneic HSCT due to the risk of graft versus host disease [8]. The conditioning regimen previous to HSCT is highly immunosuppressive and has a lymphoablative role in autoimmune diseases.

The present case report showed autologous HSTC as a safe and viable alternative for patients with severe autoimmune diseases refractory to several lines of conventional treatment. In our case, the patient has been in remission for more than five years with no medication.

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Supplementary material

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