Extracorporeal photopheresis did not prevent the development of an autoimmune disease: myasthenia gravis

Vedat Uygun,[1] Hayriye Daloğlu,[2] Seda Irmak Öztürkmen,[2] Levent Döşemeci,[3] Gülsün Karasu,[4] Volkan Hazar,[5] and Akif Yeşilipek[1]

BACKGROUND: Myasthenia gravis (MG) is a neuromuscular disorder characterized by an autoimmune defect in the neuromuscular junction. In most patients, the autoimmune attack is mediated by antibodies against the acetylcholine receptor (AChR) on the postsynaptic membrane. Deficient immunoregulation, including regulatory T cells, is consistently observed. Extracorporeal photopheresis (ECP) leads to the induction of regulatory T cells that mediate immunologic tolerance in autoimmune diseases; however, the data regarding MG are very limited.

CASE REPORT: Here, we report a patient who, during ongoing ECP therapy for his severe, refractory, chronic graft-versus-host disease (cGVHD), developed MG, although he responded very well to ECP, as indicated by the lowering of his chronic cGVHD severity grade to moderate.

RESULTS: Despite receiving ECP, our patient developed MG, which was resistant to treatment and required intensive care unit support.

CONCLUSIONS: Close surveillance is required when ECP is planned as one of the treatment alternatives in myasthenia gravis that develop in cGVHD.

Myasthenia gravis (MG) is a neuromuscular disorder characterized by an autoimmune defect in the neuromuscular junction (NMJ). In most patients, the autoimmune attack is mediated by antibodies against the acetylcholine receptor (AChR) on the postsynaptic membrane. However, antibodies other than AChR, like anti-muscle–specific receptor tyrosine kinase (anti-MuSK) and anti-low–density lipoprotein receptor-related protein 4, also may be related to this pathologic condition, and 10% of patients are negative for these antibodies.[1] Research on novel autoantibody reactivities and their pathogenic mechanisms still lead to relevant discoveries, but the study of other components of the immune response, such as innate

ABBREVIATIONS: AChR = acetylcholine receptor; cGVHD = chronic graft-versus-host disease; ECP = extracorporeal photopheresis; GVHD = graft-versus-host disease; HSCT = hematopoietic stem cell transplantation; MG = myasthenia gravis; MuSK = muscle-specific receptor tyrosine kinase; NMJ = neuromuscular junction; TPE = therapeutic plasma exchange.

From the [1]Pediatric Bone Marrow Transplantation Unit, Medical Park Antalya Hospital, Bahçeşehir University; and the [2]Pediatric Bone Marrow Transplantation Unit, Medical Park Antalya Hospital, Antalya, Turkey; and the [3]Intensive Care Unit, Istanbul Kemerburgaz University Faculty of Medicine; the [4]Pediatric Bone Marrow Transplantation Unit, Medical Park Göztepe Hospital, Bahçeşehir University; and the [5]Pediatric Hematology and Oncology and Bone Marrow Transplantation Unit, Medipol University Faculty of Medicine, Istanbul, Turkey.

Address reprint requests to: Vedat Uygun, Bahçeşehir University, Medical Park Antalya Hospital, Pediatric BMT Unit, Fener Mah, Tekelioğlu Cad. No.7 Lara, Antalya, Turkey; e-mail: veddat@hotmail.com.

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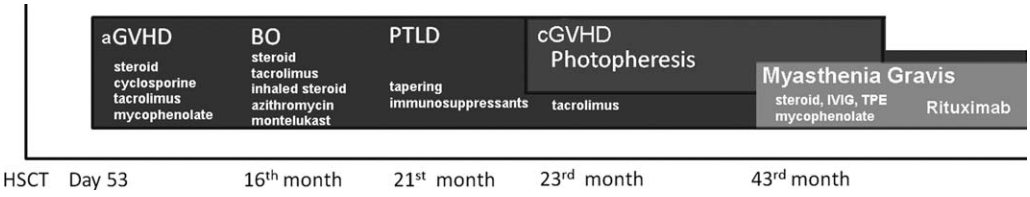

Fig. 1. Disease courses and treatments during follow-up. aGVHD = acute graft-versus-host disease; BO = bronchiolitis obliterans; PTLD = post-transplantation lymphoproliferative disorder; cGVHD = chronic graft-versus-host disease; IVIG = intravenous immunoglobulin; TPE = therapeutic plasma exchange; HCST = hematopoietic stem cell transplantation.

immunity, intrathymic mechanisms, T cells, or microRNA, is opening new insights into the development and pathogenesis of MG.[2] In general, deficient immunoregulation is consistently observed, including the abnormalities of the T cell response which have been shown by the imbalance between the different T cell subsets, including regulatory T cells.[3]

The cause of graft-versus-host disease (GVHD) includes donor T-cell alloreactivity to recipient human leukocyte antigens. GVHD frequently requires long-term, systemic immunosuppression, and extracorporeal photopheresis (ECP) is useful in combination therapies for this refractory disease. The exact mechanisms behind ECP are unclear, but murine studies indicate that ECP leads to the induction of regulatory T cells, which mediate immunologic tolerance.[4] The beneficial effect of ECP in autoimmune diseases recently has been widely discussed[5,6]; however there are very limited data regarding MG.[7]

Here, we report a patient who, during ongoing ECP therapy for severe, refractory, chronic GVHD (cGVHD), developed MG, although he responded very well to ECP, as indicated by the lowering of his cGVHD severity grade to moderate.

CASE

A 9-year-old boy who had a late diagnosis of primary hemophagocytic lymphohistiocytosis underwent peripheral blood stem cell transplantation from his serologically HLA-matched mother in January 2011. Neutrophil and platelet engraftments were observed on Days 13 and 15 post-transplantation, respectively. He engrafted with full chimerism and had no serious adverse events.

A skin rash emerged on Day 53 after transplantation, and serious diarrhea followed 1 week later despite the addition of a steroid. Because he also had protein-losing enteropathy, the patient was diagnosed with grade 3 GVHD and received treatment with combinations of pulse steroid, cyclosporine, tacrolimus, and mycophenolate. Although a response was achieved to GVHD treatment, the patient developed respiratory failure, for which he was followed in the intensive care unit for 1.5 months; later, he was transferred to the regular ward and was discharged from there on Day 162. He again was brought to our attention 16 months after transplantation for a deterioration of respiratory function tests, which revealed possible bronchiolitis obliterans. He was put on methylprednisolone, tacrolimus, inhaled steroid, azithromycin, and montelukast. With stable respiratory functions on follow-up, he also was prescribed local cyclosporine treatment for dry eye at $\geq$19 months. During this period, he started to develop erythema and sclerodermoid skin changes, and he was continuously followed with a diagnosis of cGVHD of moderate intensity. He was examined for neck swelling and severe hepatosplenomegaly at $\geq$21 months and was diagnosed with post-transplantation lymphoproliferative disorder secondary to Epstein-Barr virus. Having entered complete remission with the tapering of immunosuppressants and the addition of intravenous immunoglobulin (IVIG) treatment, the patient had increased cGVHD signs and symptoms at follow-up, and he developed severe cGVHD affecting the skin, eyes, mouth, lungs, and joints. Having previously refused photopheresis, he finally accepted it and began treatment on Day 693 post-transplantation. During that period, he received only tacrolimus as an immunosuppressant, and his treatment against bronchiolitis obliterans also continued. Photopheresis was scheduled for 2 consecutive days once a week for the first 2 months, 2 consecutive days every 15 days for the next 2 months, and once a month thereafter. After 2 months of photopheresis, a dramatic response was observed, with eye and mouth symptoms having completely resolved, skin and joint symptoms having regressed by a score of 1 score, and a trend toward improvements on respiratory function tests. The patient was scheduled for an outpatient follow-up visit while receiving tacrolimus to undergo photopheresis every month (Fig. 1).

After 20 months on photopheresis (Day 1302 after transplantation), he was re-admitted to the emergency department with ptosis and limitation of inward gaze in the right eye, reduced swallowing reflex, and paresthesia in tongue movements. A cranial magnetic resonance image revealed no pathology; the AChR antibody (anti-AChR) level was checked, and the patient was given a preliminary diagnosis of MG. Electromyography was

consistent with MG. The patient's mother (the donor) was questioned for a history of autoimmune diseases and did not report any pathology. Tacrolimus was stopped with the thought that his clinical condition was caused by neurotoxicity secondary to tacrolimus.

Because he had progressive swallowing and respiratory difficulty within a 1-day period despite supportive therapy, the patient was admitted to the intensive care unit and intubated. His anti-AChR level was 25 nmol/L ($n < 0.25$), and he was considered to have MG, for which he was started on methylprednisolone 2 mg/kg/day and IVIG 2 g/kg. In addition, he received pyridostigmine 1 mg/kg/dose, which was increased from 4 doses to 6 doses in the absence of any respiratory improvement. His anti-AChR level was reduced down to 9 nmol/L on IVIG and steroid therapy, and a computed tomography scan to detect thymoma revealed no pathology. Because the intubation period was prolonged, a tracheostomy was opened on Day 10 after admission. Sirolimus was commenced against MG and cGVHD; however, it had to be stopped 4 weeks later because of leukopenia, frequent atelectasis, pneumonia, and bacteremia at follow-up. IVIG therapy was repeated 3 weeks later; his respiratory failure improved, and he was transferred to a regular ward on Day 52 after intensive care admission.

A decision was made to continue a medical regimen with mycophenolate, methylprednisolone, pyridostigmine, and IVIG support; monthly photopheresis therapy also was applied during that period. The patient had no apparent symptoms for a while, but he presented again 120 days after the first attack with the same complaints. He rapidly deteriorated and was admitted to the intensive care unit and intubated. His anti-AChR level, which had decreased down to 6 nmol/L during outpatient follow-up, rose to 30 nmol/L in the intensive care unit. The patient did not respond to IVIG at this time; therefore, he received therapeutic plasma exchange (TPE) for 5 days every other day. Methylprednisolone 1 mg/kg/g was continued, mycophenolate was stopped, and no additional immunosuppressive treatment was started. Care was taken not to administer medications that could potentially aggravate myasthenia crisis. His need for mechanical ventilator support remained for a long time. An additional IVIG treatment as well as three more 5-day every other day courses of TPE achieved some success from time to time, although the anti-AChR level remained between 30 and 60 nmol/L, and his need for mechanical ventilator support persisted.

Although his anti-AChR level remained high at follow-up, because of the patient's psychological problems and the better general status he had achieved, it was decided to discharge him with a tracheostomy using a home ventilator on Day 135 after intensive care unit admission. However, he experienced a repeat myasthenic crisis during follow-up at the hospital ward, and his methylprednisolone dose was increased to 2 mg/kg/g. It was also planned to administer IVIG at a dose of 2 g/kg/g initially, followed by rituximab treatment. Azathiopurine 2.5 mg/kg/g also was commenced for long-term use during the same period. His neurological signs and symptoms completely resolved after IVIG therapy, and rituximab 375 mg/m^2/week was also administered for 4 weeks. The anti-AChR level after the last dose was measured at 6 nmol/L, the patient was disconnected from the mechanical ventilator, and his tracheostomy was removed to breathe in room air. Photopheresis, which had been discontinued because of the patient's poor overall condition after the second intensive care admission, was not reinstituted, because the other therapies used also were considered to be potentially effective against GVHD. The patient is receiving methylprednisolone 1.5 mg/kg/g and azathiopurine 2.5 mg/kg/g, and he is followed on room air at 4.5 years after transplantation and on Day 200 after his first myasthenic crisis.

DISCUSSION

MG is an autoimmune disease in which multifactorial predisposing factors have a role, and it develops as a result of the muscular dysfunction caused by injury to the neuromuscular junction by antibodies released by a T-cell–mediated mechanism.[8,9] By binding to AChRs, the antibodies inhibit muscular stimuli and cause inflammatory breakdown. The role of the complement system in this breakdown suggests that the mechanism responsible for the disorder is much more complex.[9] In hematopoietic stem cell transplantation (HSCT) recipients, MG develops about 22 to 60 months after transplantation, usually in the presence of signs of cGVHD; therefore, it is accepted as an "associated" manifestation of chronic GVHD.[10,11] In contrast to idiopathic cases, thymomas have not been reported as a cause in patients who undergo transplantation. Although the etiology is probably different between thymoma-associated MG and MG after allogeneic HSCT, similar mechanisms might lead to an incomplete deletion of self-specific T cells and an insufficient formation of regulatory T cells.

Although the mechanism of action of ECP is unknown, it is known that ECP plays a role in increasing regulatory T cells.[5,12,13] Therefore, in addition to cutaneous T-cell lymphoma and GVHD, its use has also been proposed in autoimmune disorders in which cytotoxic T cells take part; indeed, in some instances, it actually proved useful.[14] Despite inadequate information related to the use of ECP in MG, there have been some case reports.[7] In our case, however, MG developed despite ECP therapy against GVHD for 1.5 years. It may be speculated that such a condition, which develops as a result of T-cell–mediated antibody production, may improve or even may be abolished with a treatment modality known to provide T-cell regulation. However, our patient developed MG

despite ECP therapy coupled with tacrolimus, a drug known to inhibit T cells.

The finding of different responses to different treatments, such as anti-MuSK–related MG responding better to TPE and anti-AChR–related MG responding better to IVIG, suggest that various different mechanisms are operational in MG syndrome.[15,16] Because ECP not only provides regulatory T-cell regulation but also functions by some mechanisms yet to be agreed upon, such as the conversion of monocytes to dendritic cells, the reduction in B-cell numbers and BAAF (B-cell–activating factor), and alterations in the levels of some interleukins, it may be suggested that some mechanisms other than those in which ECP plays a role may have been active in the pathogenesis of MG.[17-19]

The physiopathology of cGVHD is not well understood. Currently, there are a few theories to explain it,[20] such as negative T-cell selection modified by thymic damage after HSCT and defective negative selection of T cells generated from bone marrow progenitors after HSCT, aberrant production of TGF-β, autoimmunity, and T-regulatory cell defect. Although donor T cells clearly play a critical role in the initiation and maintenance of GVHD, cGVHD can present as an autoimmune disease, and many laboratory and clinical studies have demonstrated that donor B cells also play an important role in the pathophysiology of cGVHD.[21] Data indicate that ECP is responsible for profound modification of the different steps and different actors involved in the immune response. The injection of apoptotic cells, obtained with ECP, modifies the pattern of cytokines, modifies the activation and function of antigen-presenting cells, and modulates the immune response.[22]

The emergence of MG during ECP therapy, as described in our patient, might be attributed to cGVHD, which may involve mechanisms separate from those in autoimmune disorders. However, it is interesting to note that, although such a clinical picture developed after severe cGVHD, it responded well to ECP. The emergence of MG during a period when a positive response indicates reduced chronic stimulation suggests a pathological condition other than independent of GVHD. Although the cause of MG is not clear in our case, we are of the opinion that at least close surveillance is required when ECP is planned as one of the treatment alternatives in MG that develop in cGVHD.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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