MYASTHENIA GRAVIS ASSOCIATED WITH THYMOMA AND APLASTIC ANEMIA: CASE REPORT

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SUMMARY – Myasthenia gravis is associated in 10 to 15 percent of patients with thymic tumors, rarely with aplastic anemia. We report a 45-year-old male diagnosed with myasthenia gravis associated with thymoma. We started treatment with pyridostigmine. After thymectomy, the patient received 30 irradiation sessions. In the postoperative course, he had mild worsening of myasthenia gravis, which improved with prednisone. Five months later, he developed severe aplastic anemia. He was dependent on blood supplement. After allogeneic transplantation of bone marrow, he improved but later he developed graft versus host disease. Myasthenia gravis was under good control with 480 mg of pyridostigmine per day.

Key words: Myasthenia gravis; Anemia, aplastic; Thymoma; Pyridostigmine bromide; Thymectomy; Prednisone; Transplantation, homologous; Graft vs host disease

Introduction

Myasthenia gravis (MG) is an autoimmune disease characterized by muscle weakness which results from blockade of the acetylcholine receptors (AChR) by antibodies and destruction of the receptors on the postsynaptic membrane. In 10 to 15 percent of patients with MG, thymic tumors occur, while in 65 percent lymphofollicular hyperplasia of the thymic medulla is found. Thymoma with malignant characteristics may spread locally into the mediastinum and to regional lymph nodes but rarely metastasizes. Thyrotoxicosis is seen in 5 percent of myasthenic patients, and other autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, mixed connective tissue disease, polymyositis and aplastic anemia can be associated with MG.

Case Report

A 45-year-old male patient was admitted because of muscle weakness, speech and swallowing difficulties and breathing problems during physical activity persisting for several months. Previous history revealed high-grade myopia (~10 and ~16 dpt); in younger age he had undergone surgical treatment of inguinal and scrotal hernia. At the age of 43, he had experienced minor head trauma with anxious depressive syndrome as a consequence, which was an obvious reason why his difficulties initially were considered as somatization. He had chronic low back pain and in 2007 thyroid adenoma with elevated T4 was found. He had lost approximately 20 kg in the previous year. He was a non-smoker and did not take alcohol.

He presented with ptosis of the right eyelid, reduced muscle strength of the right arm and both legs, and hypotrophy of both hands and shoulders. Diagnostic procedure included standard blood tests, which were normal including thyroid hormones, electrolytes and tumor markers. Brain computed tomography...
A CT scan was normal. Prostigmin test and repetitive nerve stimulation test were positive showing postsynaptic dysfunction of neuromuscular junction. While chest x-ray was normal, CT scan of mediastinum showed a thymoma, 6x3.5 cm in diameter. AChR antibodies were positive, which confirmed the diagnosis of MG. We started treatment with pyridostigmine and recommended surgical extirpation of mediastinal tumor, which was done two weeks later (Fig. 1). Histopathologic finding showed infiltration with CD3+ lymphocytes, immunohistochemical analysis showed tumor cells positive for CK7 and CK-PAN and focally positive for p-53 and bcl-2, suggesting thymoma B1 according to the World Health Organization (WHO) or predominantly cortical type according to the classification by Marino and Müller-Hermelink (Fig. 2). In the postoperative course, the patient had mild worsening of MG but improved with prednisone. Then radiation therapy in a total dose of 60 Gy in 30 fractions was administered because of infiltration of the capsule and adjacent adipose tissue with tumor cells. CT following therapy was found to be normal. Five months later, he presented with petechiae, epistaxis and gum bleeding. Laboratory findings revealed thrombocytopenia and anemia (erythrocytes (E) 2.97x10¹², hemoglobin (Hb) 86 g/L, platelets (Plt) 34x10⁹, and leukocytes (L) 7.0x10⁹). Cytologic analysis of bone marrow and peripheral blood revealed intermediate hematopoiesis with predominance of granulocytopenia, while megakaryocytes and cells of erythropoiesis were absent. Immunologic tests did not confirm autoimmune disease. Follow up CT scan of mediastinum did not show any sign of residual or relapsed tumor mass. The patient was initially treated with methylprednisolone in a dosage of 1 g/5 days, followed by immunoglobulins in a dosage of 40 g/5 days, and finally with plasma exchange but without any improvement. The patient remained transfusion dependent and developed iatrogenic diabetes, treated with gliclazide. Further treatment with azathioprine, methylprednisolone and pyridostigmine was recommended. There was no sign of MG worsening. Two weeks later, fever, respiratory infection and significant anemia and thrombocytopenia occurred. Laboratory findings showed elevated erythrocyte sedimentation rate (ESR), leukopenia, anemia and thrombocytopenia (ESR 73, L 2.5, E 2.66, Hb 87, Plt 12). Immunologic tests including antinuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), lupus anticoagulant test, cardiolipin antibodies, rheumatoid factor and complement tests were normal. Cytologic analysis of bone marrow showed normal granulocytopenia, while erythropoiesis and thrombocytopenia were absent. Treatment with rituximab 100 mg once a week was started; since no improvement was noted after 4 weeks with bleeding complications and transfusion dependence, a decision was made to proceed to bone marrow transplantation. HLA typing was done, followed by matched related allogeneic peripheral blood stem cell transplantation, with his sister being
the donor. He experienced acute graft versus host disease (GVHD), which was treated with corticosteroids. Fourteen months later, macular skin exanthema occurred. Laboratory findings were normal except for elevated liver enzymes (E 4.71, Hb 142, Plt 142, L10.85, aspartate transaminase 87 U/L, alanine transaminase 82 U/L, gamma-glutamyltransferase 437 U/L). Liver biopsy was done showing chronic active hepatitis within GVHD, which improved after corticosteroid treatment. Three months later, Epstein-Barr (EBV) viremia was found and he received rituximab until viral clearance, in order to prevent posttransplantation lymphoproliferative disease. MG remained under good control over the mentioned period with 480 mg of pyridostigmine per day.

Discussion

We report a case of a 45-year-old male patient with a complex autoimmune neuromuscular disorder associated with thymoma and complicated with severe aplastic anemia after thymectomy, which was refractory to standard medical treatment with corticosteroids, immunoglobulins and plasma exchange. It is well known that thymoma can be complicated with MG and that MG is associated with thymoma, but development of aplastic anemia in these patients is a rare condition. Aplastic anemia usually precedes the diagnosis of thymoma. There have been only three cases described in the literature of aplastic anemia occurring as a late complication after thymectomy with the time interval between 3 and 48 months. Ritchie et al. described a single case of MG and aplastic anemia after thymectomy and remission of thymoma. Suzuki et al. found that 4 of 135 (2.9%) patients with MG had pure red cell aplasia (PRCA) after thymectomy. PRCA is also known as a concomitant disorder with MG. They concluded that thymoma, bulbar involvement and high level of AChR antibodies were significantly higher in patients with PRCA. Kobayashi et al. report a case of a patient with MG, thymoma, thrombocytopenia and granulocytopenia. After thymectomy, not only the symptoms of MG but also hematologic findings improved. They also found that serum level of p-ANCA against myeloperoxidase of granulocytes dramatically decreased after thymectomy, showing significant correlation with the granulocyte count. Conclusion was that p-ANCA could be regulated by thymoma, leading to severe granulocytopenia. According to the staging system, thymomas are classified as stage I when completely encapsulated, stage II when extending through the capsule and with pericapsular fat invasion, stage III when characterized by invasion of adjacent structures, and stage IV when showing thoracic dissemination or metastases. The classification by Marino and Müller-Hermelink distinguishes medullary, mixed, predominantly cortical, cortical thymoma, well-differentiated thymic carcinoma, and other rare types of thymic carcinoma. These types differ according to invasiveness, prognosis and association with MG. Medullary and mixed thymomas are rarely associated with MG, while medullary type is most frequently associated with hematologic disorders. Cortical thymoma affects younger patients, shows more invasive nature, and is more frequently associated with MG. The occurrence of MG in a patient with thymoma usually precedes the diagnosis of thymic neoplasm. In the Mayo Clinic, 40% of 283 patients presented with symptoms of tumor at the time of diagnosis, while 46% presented with symptoms of MG. Out of these patients, 29% had symptoms directly related to tumor.

Complete surgical resection is the gold standard in the treatment of thymoma. However, in advanced stage, complete resection may be difficult and recurrence is often recorded. In such cases, chemo- and radiotherapy after surgical treatment improve the prognosis. Also, in a tumor that is considered inoperable, induction radiotherapy applied before surgery improves the outcome. In a retrospective study, Vassiliou et al. showed that patients with MG and thymoma had a favorable outcome and that radiotherapy could be omitted in totally resected stage I-II patients, whereas it was beneficial in more advanced stages. On the other hand, Mangi et al. showed that radiation did not prevent pleural recurrences in stage III.

The course of the disease in the patient we presented is interesting because he had MG associated with thymoma and aplastic anemia as a late complication after thymectomy and remission of thymoma including a list of severe immune complications after allogeneic bone marrow transplantation. Despite hematologic, immunologic and infectious complications, prolonged corticosteroid treatment probably had a favorable effect on his neuromuscular disorder, since his MG showed no signs of worsening over time.
References


Sažetak

MIASTENIJA GRAVIS UD RUŽENA S TIMOMOM I APLASTIČNOM ANEMIJOM: PRIKAZ SLUČAJA

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Miastenija gravis (MG) je u 10% do 15% bolesnika udružena s tumorima timusa, rijetko s aplastičnom anemijom. Prikazu još 45-godišnjeg bolesnika s MG udruženom s timomom. Liječenje je započeto piridostigminom. Nakon timektomije je provedeno 30 zračenja. Poslijeoperacijski je imao blago pogoršanje MG koje se povuklo uz terapiju prednizonom. Pet mjeseci kasnije je razvio tešku aplastičnu anemiju. Postao je ovisan u krvnim derivatima. Nakon alogenične transplantacije kostne srži došlo je do poboljšanja, ali je kasnije razvio reakciju transplantata protiv primatelja. MG je bila dobro kontrolirana už 480 mg piridostigmina na dan.

Ključne riječi: Miastenija gravis; Anemija, aplastična; Timom; Piridostigmin bromid; Timektomija; Prednison; Transplantacija, homologna; Transplantacijska bolest