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Case report

Myasthenia gravis without chronic GVHD after allogeneic bone marrow transplantation

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Summary:

A 20-year-old man with aplastic anemia developed myasthenia gravis (MG) 7 months after bone marrow transplantation (BMT) from an HLA one locus-mismatched sister. Proximal muscle weakness (predominant in the lower limbs) and dysphagia occurred without any other sign of graft-versus-host disease (GVHD), 1 month after cessation of immunosuppression with cyclosporine. The diagnosis of MG was based on clinical symptoms and on neurophysiologic investigations showing a significant increase of the Jitter in single-fiber electromyography and a significant decremental response during repetitive stimulation at slow rates, but antibodies against the acetylcholine receptor (AchRab) were negative. All clinical and neurophysiological signs normalized within 1 month of treatment with low-dose prednisolone and pyridostigmine, and the patient is perfectly well 1 year after cessation of all therapy. All cases of BMT-associated MG previously published are reviewed in comparison with ours. The originality of this new observation is that this case is the only one not associated with chronic GVHD and negative for AchRab. Alternatively, MG may have been the sole manifestation of chronic GVHD in this patient.
Keywords: myasthenia gravis; bone marrow transplantation; aplastic anemia

The first case of myasthenia gravis (MG) following bone marrow transplantation (BMT) was described in 1983.[1] Since then, 14 cases of BMT-associated MG have been reported (Table 1).[2–12] In all these cases other signs of chronic graft-versus-host disease (GVHD) developed during the post-transplant period and antibodies to the acetylcholine receptor (AchRab) were always positive when tested. We report a new case of BMT-associated MG which developed shortly after cessation of immunosuppressive therapy without any other sign of GVHD and without AchRab.

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Case report

A 20-year-old man was diagnosed in December 1993 with severe aplastic anemia (SAA). After failure of treatment by steroids and vitamin supplements (B6, B12, folic acid), the patient was referred to us for a BMT procedure from an HLA one locus-mismatched sister who had had two pregnancies but no transfusions. The recipient's HLA typing was A10(26), A11; B8, B12(45); Cw6, Cw7; DR3, DR8; and the donor's was A10(26), A1; B8, B12(45); Cw6, Cw7; DR3, DR8. High-resolution class II molecular typing was: DPB 0401, 0101 in recipient, and 0401, 0301 in donor; DQB 0201, 0402 in both; DRB1 0301, 0801 in both. The mother was fully identical with the donor and the father's HLA typing was: A1, A11; B8; Cw7; DR3; DPB 0301, 0101; DQB 0201; DRB 0301. After conditioning with cyclophosphamide (200 mg/kg) and ATG (30 mg/kg), the patient received an unmanipulated marrow. GVHD prophylaxis was carried out with 'short' methotrexate and cyclosporine.

The immediate post-transplant course was uneventful and the patient was discharged on day 27 taking daily cyclosporine. He regularly attended the outpatient clinic and did not experience significant complications. He never developed any sign of acute or chronic GVHD. Routine skin and mucosa biopsies, as well as Shirmer tests at day 100 and day 180, were negative. After tapering, cyclosporine was discontinued on day 180. Cytogenetic analyses of bone marrow cells at days 100, 180 and 365 showed a normal female karyotype (46,XX). FISH analysis of more than 1500 nuclei with probes for the X and Y chromosomes failed to detect any Y chromosomes. The patient was in excellent physical shape and had resumed intensive training in several sports.

Around day 210, he developed abnormal fatigue and proximal muscle weakness predominant in the lower limbs. He had serious difficulties in going up stairs, rising from a chair or from bed and in swallowing. General physical examination was normal. Upon neurological examination, we noticed diffuse moderate muscle atrophy of the legs. The deep tendon reflexes were all brisk and symmetrical

Table 1 Reported cases of BMT-associated MG

Case No. *Author*	*1* *Baron*	*2* *Smith*	*3* *Bolger*	*4* *Bolger*	*5* *Bolger*	*6* *Grau*	*7* *Shimoda*	*8* *Zaja*	*9* *Seely*	*10* *Adams*	*11* *Atkinson*	*12* *Haslam*	*13* *Melms*	*14* *Lefvert*	*15* *Abecassis*
Patient/donor															
Sex	M/F	F/M	F/F	F/F	M/–	M/F	M/M	M/F	M/F	M/F	M/F	M/M	M/F	NR	M/–
Age	20/30	12/–	9/–	9/–	13/–	26/23	37/–	30/35	19/–	6/–	20/–	37/–	22/–	NR	19/–
HLA A/A	11,26/1,26	3,2/3,2	28,24/28,24	2,31/2,31	NR	2,11/2,11	31,26/24,26	2/2	NR	NR	NR	11,25/11,25	2,3/2,3	NR	NR
B/B	8,12/8,12	40,7/40,7	35,7/35,7	35,40/35,40	NR	35,56/35,56	7/7	5,16/5,16	NR	NR	NR	39/39	7,60/7,60	NR	NR
Cw/Cw	6,7/6,7	NR	NR	NR	NR	1,4/1,4	7/7	1,4,6/1,4,6	NR	NR	NR	NR	7/7	NR	NR
DR/DR	3,8/3,8	4,2/4,2	2/2	NR	NR	NR	1,9/1,9	NR	NR	NR	NR	1,5/1,5	2/2	NR	NR
Disease	SAA	SAA	SAA	SAA	NHL	ALL	CML	AML	SAA	SCID	SAA	AML	SAA	SCID	CML
Conditioning	Cy+ATG	Cy	Cy+ATG	Cy+Bu	NR	Cy+TBI	Cy,AraC,TBI	Cy+Bu	NR	NR	Cy	Cy+TBI	NR	NR	NR
GHVD prophylaxis	CSP+MTX	MTX	MTX	MTX	NR	MTX	CSP+MTX	CSP	NR	NR	CSP	CSR+MTX	NR	NR	NR
Chronic GVHD															
Yes/no	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[a]	Yes	Yes	NR
Timing relative to MG		preceding	simultaneous	preceding	NR	preceding	simultaneous	simultaneous	simultaneous	preceding	preceding	NR	NR	NR	NR
Treatment		PDN+AZA	PDN+AZA	PDN+AZA	PDN	PDN+AZA	PDN+CSP	PDN+AZA +CSP	PDN+AZA	PDN+CSP	PDN+CSP	NR	PDN+CSP	NR	NR
Current immuno-suppression	CSP tapered and stopped 1 mo before	PDN+AZA	PDN 5 mg/d and AZA	PDN 10 mg/d	PDN tapered	PDN stopped 1 mo before	Sudden cessation of PDN and CSP shortly before	PDN+AZA +CSP Low dose CSP and PDN	PDN+AZA	PDN	PDN	CSP stopped 7 mo before	Tapered	NR	NR
MG															
Month post BMT	7	27	35	24	26	46	29	46	35	36	27	11	60	7	3
Symptoms	PMW, DIS	Pto, Dip	PMW, DIS, Pto, Dys, RF	PMW, Pto, Dys, RF	PMW, RF	PMW, DIS, Dip, Dys	PMW, DIS, Pto	PMW, Pto, Dip	NR	PMW, DIS, Pto	PMW, Dys	PMW, Pto, Dip	PMW, DIS, Dip	NR	PMW, Pto, Dip
Ventilation	no	yes	yes	no	yes	no	no	no	NR	no	no	NR	no	NR	NR
Osserman group	2A	1	2B	3	3	2B	2A	2A	NR	2B	2A	2A	2A	NR	2A
EMG															
DRLF	Yes	NR	yes	no	yes	yes	NR	yes	yes	yes	NR	NR	NR	NR	NR
Jitter phenomenon	Yes	Yes	NR	NR	NR	yes	NR	NR	NR	NR	NR	NR	NR	NR	NR
Edrophonium test	NR	+	+	+	+	+	NR	NR	+	+	NR	+	NR	NR	+
AchRab	–	+	+	+	+	+	+	+	+	+	+	+	+	+	NR
Chest X-ray or CT scan	Normal	NR	Normal	Normal	NR	Normal	Normal	Normal	Normal	NR	Lung fibrosis	Normal	NR	NR	NR
Treatment															
Pyridostigmine	yes	yes	yes	yes	yes	yes	no	yes	yes	yes	yes	yes	yes	NR	NR
Steroids	yes	no	yes	yes	yes	yes	yes	yes	no	yes	yes	yes	yes	NR	NR
CSP	no	no	no	no	no	no	yes	yes	no	yes	yes	no	no	NR	NR
Azathioprine	no	no	yes	no	yes	yes	no	no	no	no	no	no	no	NR	NR
Plasmapheresis	no	no	yes	no	yes	no	no	no	no	yes	no	no	no	NR	NR
Evolution															
Resolved	yes	improved	yes	yes	NR	yes	yes	yes	NR	no	no	yes	yes	NR	NR
Therapy stopped	yes	no	yes	no	NR	no	NR	tapered	NR	NR	no	yes	NR	NR	NR
Relapse	no	no	yes	no	NR	no	NR	yes	NR	NR	stable	no	NR	NR	NR
Follow-up	14 mo	9 mo	50 mo	7 mo	NR	NR	NR	9 mo	NR	36 mo	8 mo	NR	NR	NR	NR

PMW = proximal muscle weakness; DIS = difficulty in swallowing; Pto = ptosis; Dip = diplopia; Dys = dysarthria; RF = respiratory failure; PDN = prednisolone; AZA = azathioprine; CSP = cyclosporine; MTX = methotrexate; Cy = cyclophosphamide; Bu = busulfan; Ara-C = arabinoside cytosine; ATG = antithymocyte globulin; NR = not reported; DRLF = decremental response to low frequencies.
[a]Subclinical chronic GVHD was probably present.

and the plantar responses were flexor. Sensation to light touch, pinprick and vibration, as well as examination of cranial nerves, were normal. Electrophysiological testing showed normal nerve conduction but a significant decremental response during repetitive stimulation at a rate of 3 per second (14% in the anconeus muscle). Single fiber electromyography resulted in an increased Jitter value in the extensor digitorum communis muscle. A diagnosis of MG was established despite negativity of the AchR antibody. Hematological parameters were normal. Antithyroglobulin antibodies were positive at a titer of 1/76, while antinuclear, antismooth muscle, antimitochondrial and antimicrosomial antibodies were negative. Both chest X-ray films and CT scan were normal. There were no signs of chronic GVHD. The patient was started on 24 mg/day prednisolone and 3×60 mg/day pyridostigmine. This therapy produced prompt resolution of his symptoms and electrophysiological testing performed 2 months later was normal. Treatment was stopped by the patient after 2 months as he felt totally normal. He has remained in clinical and electrophysiological remission for more than 1 year, and has not developed any degree of chronic GVHD.

Discussion

The complaints and clinical presentation of this patient are compatible with a Lambert–Eaton syndrome but certainly not specific for it. Furthermore, there was no recovery of power after a series of several voluntary contractions. Electrophysiology was incompatible with that diagnosis. Compound motor unit action potentials did not have a low amplitude after a single stimulus. At fast rates of stimulation, there was no increase in the amplitude of action potentials. Single fiber electromyography did not show Jitter increase when reducing the frequency of stimulation, a characteristic of Lambert–Eaton syndrome. We therefore believe that a Lambert–Eaton syndrome was excluded.

The incidence of MG is increased at least 20 times after BMT compared to that seen in the general population.[4] We described here the 15th such case.[1–12] However, this figure is most probably an underestimate since fatigue is a common manifestation of chronic GVHD and treatment of chronic GVHD should be effective in suppressing symptoms of MG in mild cases.[4] It is not known which BMT patients are at risk of MG.[3,6,8,10] Idiopathic MG is age- and sex-related, with one peak incidence affecting mostly women in the second and third decades and another mostly men in the sixth and seventh decades.[13] An HLA haplotype with B8/DR3 has been associated with early-onset MG, B7/DR2 and late-onset MG and B35/DR1 with penicillamine-induced MG. Surprisingly, in most BMT cases, patients were young (6–37 years) males (11 of 14 cases), the donors were of the opposite sex (eight of 11 cases), and the underlying disease was aplastic anemia (seven of 15 cases). HLA data reported in nine cases showed no association with these or other haplotypes. This may indicate that the pathophysiology of BMT-associated MG differs from other forms of MG. In six cases including ours, MG developed after discontinuation or tapering of long-term immunosuppression and in all cases before ours, MG was associated with AchRab and chronic GVHD. However, the finding of AchRab after twin or autologous BMT may constitute evidence against an important role of GVHD in this autoimmune complication.[14] Moreover, a negative association (not statistically significant) was found between the presence of AchRab and chronic GVHD.[4]

The diagnosis of MG is based on a typical clinical picture, a characteristic electromyographic pattern, a positive response to cholinesterase inhibitors, and the presence of AchRab.[13] A clinical classification has been proposed, based on the distribution and severity of symptoms: group 1, ocular; group 2A, mild generalized; group 2B, moderately severe generalized; group 3, acute fulminating; group 4, late severe. Among the 12 evaluable post-BMT cases, one patient was in group 1, six (including ours) in group 2A, three in group 2B and two in group 3. Contrary to typical MG, BMT-associated MG has not been associated with thymic abnormalities and the study of other auto-antibodies failed to uncover consistent findings. A drop in amplitude of the evoked muscle action potential in repetitive nerve stimulation at a rate of 2 or 3 per second (decrement $\geqslant$10% between the first response and the smallest of the next four responses) and an increased Jitter value in single-fiber EMG are the two typical EMG findings. MG is an autoimmune disease in which antibodies against the acetylcholine receptor can be detected. However, about 10–20% of MG patients do not have detectable AchRab, including patients with generalized weakness whose disease corresponds to conventional MG with respect to other clinical, diagnostic, and therapeutic features.[13] These patients probably have antibodies directed at epitopes not present in the soluble AchR extract.[13] Our patient must be included in this group contrary to all other cases of BMT-associated MG. Furthermore, the presence of AchRab without MG has been demonstrated in many BMT recipients,[4,14] possibly a manifestation of subclinical host–recipient interactions. However, such antibodies have even been detected in patients with various hematologic disorders not undergoing BMT.[15]

Therapy of MG following BMT is based on pyridostigmine and on treatment of the GVHD process by prednisolone, azathioprine and/or cyclosporine. The prognosis is generally good (MG resolved in eight of 10 patients and improved in one) but three patients required plasmapheresis for life-threatening problems, two relapsed and one was still requiring pyridostigmine, prednisone and cyclosporine 8 years later. Our patient received treatment with low-dose prednisolone and pyridostigmine for only 2 months, with complete resolution of all clinical and EMG signs. MG must therefore be suspected when BMT recipients complain of neuromuscular symptoms even in the absence of signs of chronic GVHD.

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