Progressive Weakness after Stem Cell Transplant

Ryan D. Jacobson MD

A 72-year-old psychiatrist presents for evaluation of worsening muscle weakness, occurring two months following an autologous stem cell transplant.

Past Medical History

- **Myasthenia gravis:**
  - Diagnosed with ocular myasthenia gravis 10 years prior
  - Presented with intermittent, unilateral ptosis
  - Unsure if he was antibody positive or not
  - Took occasional doses of pyridostigmine when ptosis more noticeable
  - Has not taken any medication or noticed any symptoms since his cancer diagnosis

- **Multiple Myeloma:**
  - Diagnosed 6 months prior after a pathologic hip fracture
  - Underwent chemotherapy (velcade, revlimid, dexamethasone), finishing 2 months prior
  - Underwent autologous PBSCT 2 months prior (melphalan induction. Hospital course complicated by cryptosporidiosis).
  - Now thought to be in remission

History of Present Illness

- Reports 10 – 14 days of progressive weakness
- Finds that his “neck is droopy” and he cannot hold it up
- Feels weak in his shoulders and hips
- Short of breath with exertion, and difficulty lying flat. Generally fatigued.
- Denies ptosis, diplopia, dysarthria, dysphagia
- Has lost about 20 pounds since transplant

Examination

Cranial nerves:
No ptosis. Eye movements full. Eye closure strong. Cheek puff strong. No dysarthria.

Motor:

Neck flexion 4/5
Neck extension 4/5

Upper Extremities

	Right	Left
Deltoids	4/5	4/5
Infraspinatus	4/5	4/5
Biceps	4+/5	4+/5
Triceps	4+/5	4+/5
Wrist extensors	5/5	5/5
Wrist flexors	5/5	5/5
Finger extensors	5/5	5/5
Deep finger flexors	5/5	5/5
Finger abduction	5/5	5/5
Thumb abduction/APB	5/5	5/5

Lower Extremities

	Right	Left
Hip flexion	4/5	4/5
Knee flexion/hamstrings	4/5	4/5
Knee extension/quadriceps	5/5	5/5
Ankle dorsiflexion/A.T.	4-/5	5/5
Ankle inversion	5/5	5/5
Ankle eversion	4-/5	5/5
Plantar flexion	5/5	5/5
Great toe extension	4-/5	5/5

Sensory:
Light touch, pinprick sensation normal throughout.

Reflexes:
Muscle stretch reflexes 2+ and symmetric at hte bilateral biceps, triceps, brachioradialis, patellae and ankles.
Plantar responses flexor.

Gait:
Unable to arise from a chair without use of arms.
Steppage appearance on the right

Laboratories

11/10/2017 1:32 AM - Interface, Lab Results

Component Results

Component	Value	Ref Range & Units	Status
SODIUM	137	136 - 144 mmol/L	Final
POTASSIUM	4.3	3.3 - 5.1 mmol/L	Final
CHLORIDE	108	98 - 108 mmol/L	Final
CO2	22	20 - 32 mmol/L	Final
ANION GAP	7	4 - 16	Final
BUN	18	7 - 22 MG/DL	Final
CREATININE	0.86	0.6 - 1.4 MG/DL	Final
GLUCOSE	92	70 - 100 MG/DL	Final
ALBUMIN	3.0 ⌄	3.6 - 5.0 GM/DL	Final
PROTEIN, TOTAL	5.5 ⌄	6.5 - 8.3 GM/DL	Final
CALCIUM	8.7	8.5 - 10.5 MG/DL	Final
ALKALINE PHOSPHATASE	50	30 - 110 IU/L	Final
ALT (SGPT)	96 ⌃	10 - 40 IU/L	Final
AST (SGOT)	113 ⌃	15 - 45 IU/L	Final
BILIRUBIN,TOTAL	0.6	0.2 - 1.4 MG/DL	Final
ESTIMATED GFR	>60	>60 ML/MIN/1.73M2	Final

11/9/2017 8:15 PM - Interface, Lab Results

Component Results

Component	Value	Ref Range & Units	Status
CK	1,218 ⌃	50 - 320 IU/L	Final

EMG/NCS

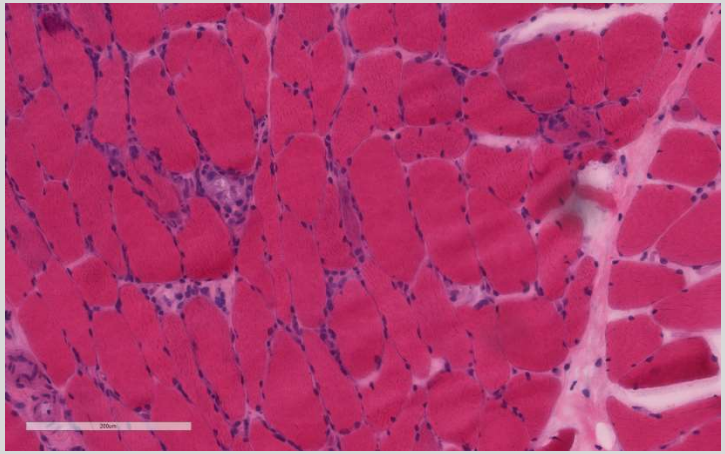
MNC

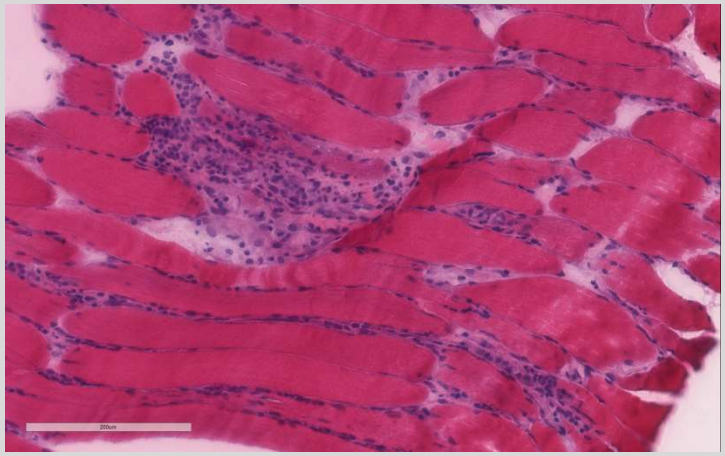
Nerve / Sites	Muscle	Latency ms	Amplitude mV	Distance mm	Lat Diff ms	Velocity m/s
R Ulnar - ADM						
Wrist	ADM	3.02	4.1	70		
B.Elbow	ADM	7.24	4.2	206	4.22	48.8

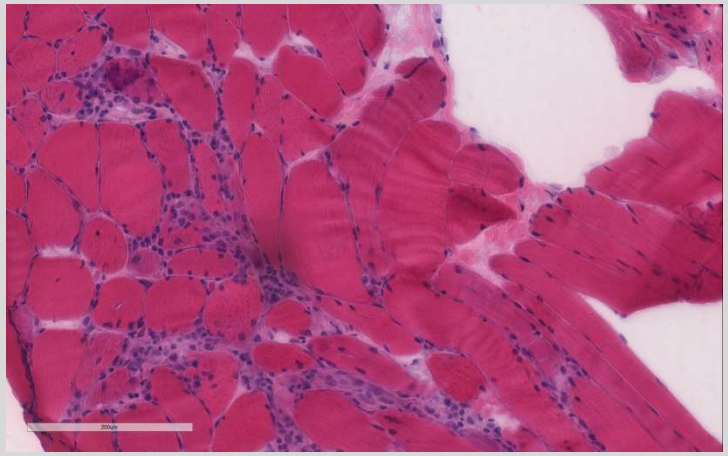
Rep Stim

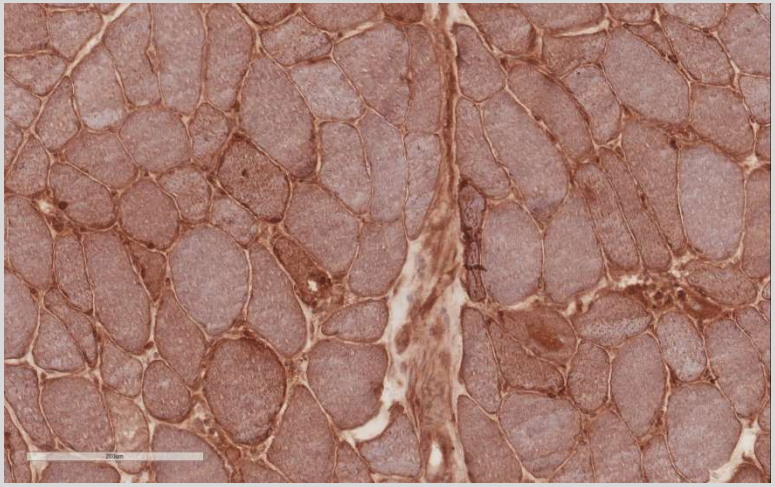
Anatomy / Train	Rate Hz	Ampl. mV	Ampl 4-1 %	Fac Ampl %	Area mVms	Area 4-1 %	Fac Area %	Time
R Abductor digiti minimi (manus) - UlnarRepStimRJ								
1	3	3.8	18.8	100	15.5	17.8	100	0:00:00
2	3	4.1	14.8	109	15.7	8.8	101	0:01:06
3	3	3.8	11.2	101	15.6	6.1	100	0:01:58
4	3	3.8	14.8	101	15.0	16.6	96.9	0:03:53

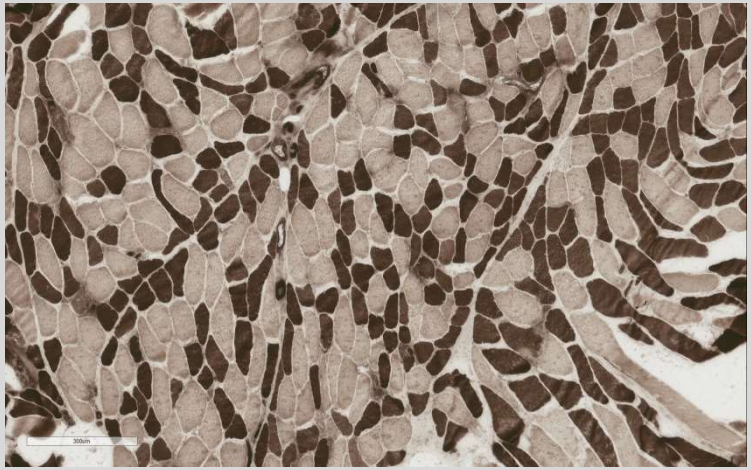
EMG Summary Table											
	Insertion	Spontaneous				Volitional MUAPs					Comments
Muscle	Activity	Fibs	PSW	Fasc	Other	Effort	Recruit	Dur	Amp	Poly	.
R. Deltoid	Increased	1+	1+	None	.	Normal	Normal	Decr	Normal	None	.
R. Triceps brachii	Increased	1+	1+	None	.	Normal	Normal	Normal	Normal	None	.
R. Vastus medialis	Increased	1+	1+	None	CRD	Normal	Normal	Normal	Normal	None	.
R. Iliopsoas	Increased	1+	2+	None	CRD	Normal	Normal	Normal	Normal	None	.
R. Gastrocnemius (Medial head)	Increased	1+	2+	None	.	Normal	Normal	Normal	Normal	None	.
R. First dorsal interosseous	Increased	0	2+	None	.	Normal	Normal	Normal	Normal	None	.
R. Thoracic paraspinals	Increased	2+	1+	None	.	Normal					.











Additional Laboratories

1

Component	Value	Ref Range & Units
ACETYLCHOLINE REC BINDING AB	1.56 ^	nmol/L

2

Striated Muscle Antibodies, IgG Screen

Striated Muscle Antibodies, IgG	**Detected**	H	<1.40

Striated Muscle Antibodies, IgG Titer	**1:1280**	**H**

3

Test	Result	Flag	Ref Range
Titin Antibody	2.50	H	0.00-0.45 IV

INTERPRETIVE INFORMATION: Titin Antibody

Negative ..... 0.00 - 0.45 IV
Indeterminate ... 0.46 - 0.71 IV
Positive ..... 0.72 IV or greater

The presence of titin antibody is associated with late onset of myasthenia gravis (MG) and a variable risk for thymoma. Titin antibody may be detected in 20-40 percent of all patients with MG; higher frequency in older population as a whole.

Final Diagnosis?

Concurrent/overlapping myasthenia gravis and myositis following autologous stem cell transplant

More questions than answers!

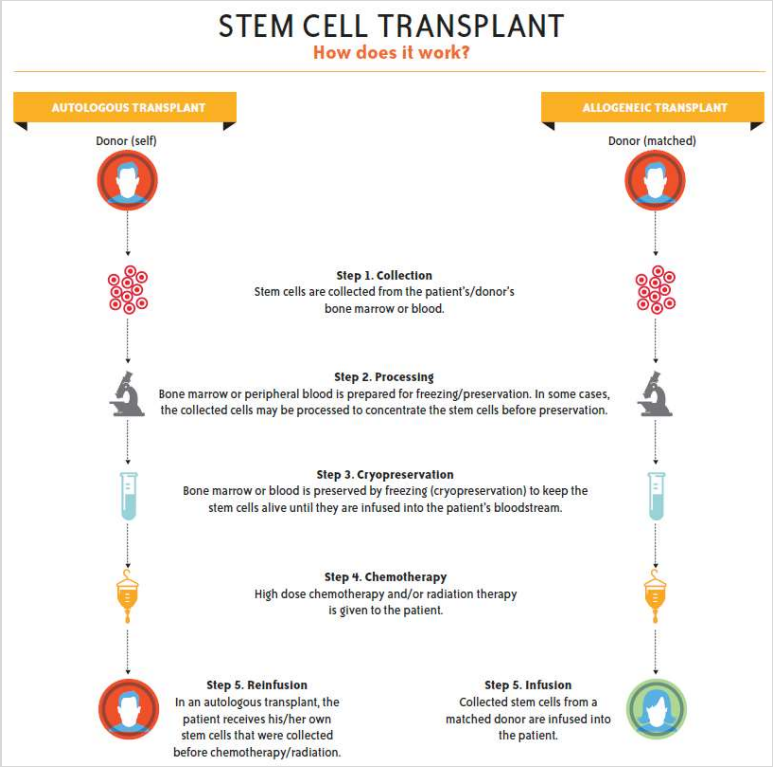
(Also, right peroneal mononeuropathy, presumably compressive)

Questions & Teaching Points

Complications of Stem Cell Transplant?

Myositis & Myasthenia Overlap?

Neuromuscular Complications of SCT



Courtesy vicc.org

cGVHD complications may include **polymyositis**, dermatomyositis, AIDP, MG.

Chronic immunosuppression is needed for allogeneic transplants.

Graft versus host disease manifestations should not be possible in autologous transplants.

"Autologous GVHD" manifestations are possible. Etiology unclear with various forms of immune dysregulation postulated.

Most common neurologic complication of autologous SCT: subdural hematoma

June 1990 NEUROLOGY 40 1003

Polymyositis following autologous bone marrow transplantation in Hodgkin's disease

J.W. Schmidley, MD, and Pamela Galloway, MD

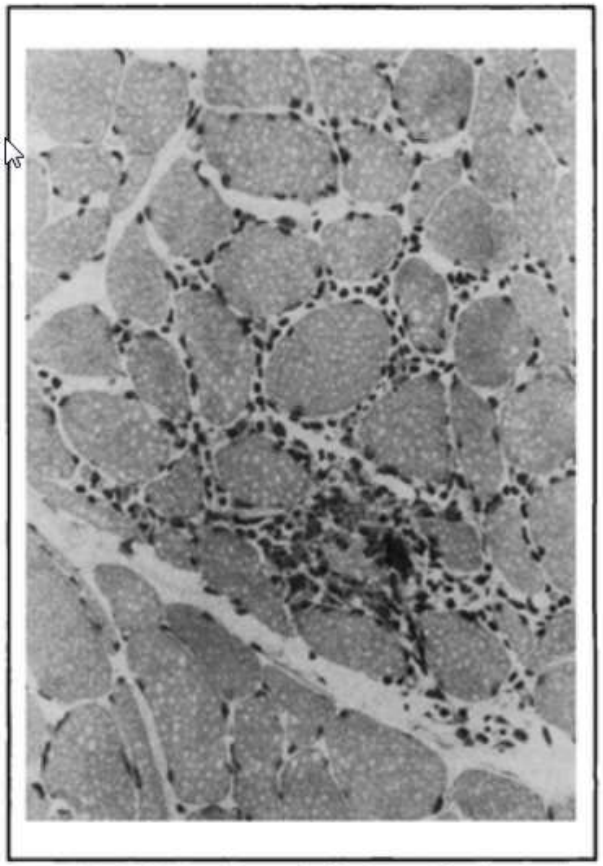


Figure. Muscle biopsy with necrotic fiber (arrow), lymphocytes in the endomysium, and variability in fiber size and shape (H-E, ×125 before 15% reduction).

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Polymyositis following autologous haematopoietic stem cell transplantation

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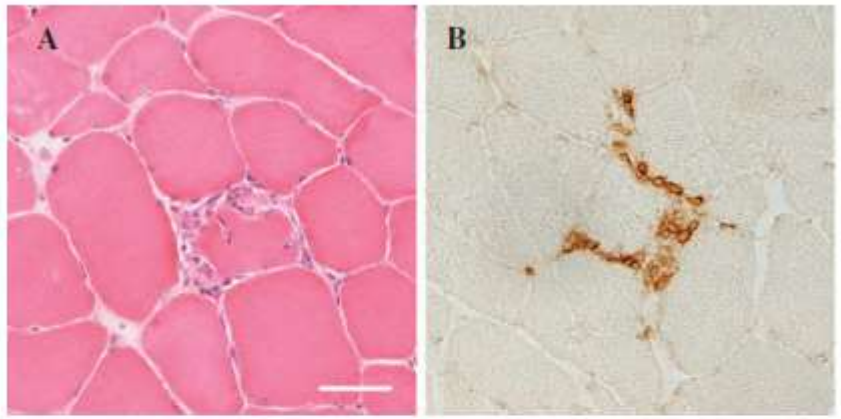

Figure 1. Biopsy slides from the vastus lateralis muscle showing (A) mononuclear cell infiltration and invasion of a non-necrotizing muscle fibre on staining with haematoxylin and eosin (H&E), and (B) the presence of multiple T lymphocytes in these infiltrates on staining with CD8 monoclonal antibodies (clone 4B11, Vector Laboratories, Burlingame, CA, USA) in a dilution of 1:40. A few macrophages were also present in CD68 monoclonal antibody staining (KP1, Vector Laboratories) at a dilution of 1:100. The inflammation was entirely endomysial, without the presence of vacuoles, regenerating fibres, angular dennervated fibres, or perifascicular atrophy. Bar is 50 µm.

Patient had distal UE weakness, proximal LE weakness. Treated with prednisone followed by IVIg.

Myasthenia & Myositis Overlap

- Fairly rare
- Described in several case series and case reports

The co-existence of myasthenia gravis in patients with myositis: A case series

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- 6 patients with both MG and myositis
- 5 of 6 had prominent bulbar symptoms
- Only 1 patient had diplopia, 2 had ptosis
- High-dose steroids worsened weakness in 2 patients

Table 1
Previously described cases of myositis–MG overlap

References	No. of cases	Age	Gender	Myositis type	Treatment
Seton et al [19]	1	46	F	PM	Steroids and pyridostigmine; surgery for thymoma
Hill et al. [18]	1	67	F	DM	Steroids and IVIG
Yoshidome et al. [17]	1	62	F	PM	Steroids and IVIG
Avni et al. [16]	1	66	M	PM	Steroids and IVIG
Shichijo et al. [15]	1	57	M	DM	Steroids
Van de Warrenburg et al. [14]	1	28	F	DM	Steroids and pyridostigmine
Otton et al. [13]	1	71	M	PM	Steroids and azathioprine
Ko et al. [12]	1	25	F	PM	Steroids, pyridostigmine, and azathioprine
Hausmanovwa-Petrusewicz et al. [11]	1	58	F	DM	Steroids and pyridostigmine
Diaco et al. [10]	1	47	F	PM	Steroids, methotrexate, then cyclosporine PM; for myasthenia gravis: pyridostigmine and surgery for thymoma
Kornizky et al. [9]	1	69	F	PM	Steroids and methotrexate
Raschilas et al. [8]	1	66	F	PM	Steroids and pyridostigmine
Kobayashi et al. [7]	1	14	F	PM	Ambenonium, thymectomy, and steroids
Hassel et al. [6]	1	37	M	PM	Thymectomy, steroids, cyclosporine, and plasma exchange
Davis and Gallai [5]	1	71	F	PM	Pyridostigmine, prostigmine, and steroids
Vasilescu et al. [4]	4	18, 24, 42, and 46	3 F and 1 M	DM	Steroids and prostigmine
De Reuck et al. [3]	1	23	M	PM	Pyridostigmine and steroids

ORIGINAL CONTRIBUTION

Autoimmune Targets of Heart and Skeletal Muscles in Myasthenia Gravis

ARCHIVES EXPRESS

Shigeaki Suzuki, MD, PhD; Kimiaki Utsugisawa, MD, PhD; Hiroaki Yoshikawa, MD, PhD; Masakatsu Motomura, MD, PhD; Shiro Matsubara, MD, PhD; Kazumasa Yokoyama, MD, PhD; Yuriko Nagane, MD, PhD; Takahiro Maruta, MD, PhD; Takashi Satoh, PhD; Hideki Sato, MD; Masataka Kuwana, MD, PhD; Norihiro Suzuki, MD, PhD

- 8 patients with MG and inflammatory myopathy or myocarditis: 3 with myocarditis, 6 with myositis
- 4 patients had invasive thymoma
- Myositis developed “before or at same time” as MG

Pathogenesis of Myositis and Myasthenia Associated with Titin and Ryanodine Receptor Antibodies

GEIR OLVE SKEIE, FREDRIK ROMI, JOHAN A. AARLI, PÅL TORE BENTSEN, AND NILS ERIK GILHUS

Department of Neurology, University of Bergen, Bergen, Norway

- Titer correlates with MG disease severity
- Tend to have more myopathic-appearing EMGs
- Tend to respond less robustly to thymectomy,

yet ---

- Present in 95% of thymoma patients
- 7 had anti-striational antibodies
  - 5 anti-Titin
  - 6 anti-RYR

Myasthenia & Myositis Overlap: Take Home Points

- Inflammatory myopathies rarely occur in MG
- There is an association with thymoma
- Often have onset around the same time
- Bulbar and neck weakness may be prominent
- Anti-striational antibodies are common, with both titin and RYR antibodies described in this population

Treatment & Outcome

- Prednisone: escalating daily doses up to 20 mg
- IVIg: 2 g/kg in hospital, followed by 1 g/kg every 2 weeks

- Weakness improved over 2-3 weeks.
- Dyspnea improved. Neck strength improved.
- Three months later: strong, working full time in psychiatry practice, occasional neck fatigue in the evenings, mild residual R foot drop.
- Remains on prednisone 7.5 mg daily, IVIg 1 g/kg every 3 weeks.
- CT: no thymoma

Final Thoughts

- Patient had both myasthenia and myositis, which is itself rare
- Occurrence of this presentation years following ocular MG diagnosis is odd
- Unclear why this occurred following an autologous stem cell transplant, but presumably a mechanism of immune dysregulation

THANK YOU!

REFERENCES

1. Adams C, August CS, Maguire H, Sladky JT. Neuromuscular complications of bone marrow transplantation. Pediatr Neurol. 1995;12(1):58-61.

2. Batra A, Cottler-Fox M, Harville T, Rhodes-Clark BS, Makhoul I, Nakagawa M. Autologous Graft versus Host Disease: An Emerging Complication in Patients with Multiple Myeloma. Bone Marrow Res. 2014;2014:891427.

3. Hedermann G, Marquart HV, Vissing J. Polymyositis following autologous haematopoietic stem cell transplantation. Scand J Rheumatol. 2016;45(5):429-431.

4. Mathew RM, Rosenfeld MR. Neurologic Complications of Bone Marrow and Stem-cell Transplantation in Patients with Cancer. Curr Treat Options Neurol. 2007;9(4):308-314.

5. Mygland A, Vincent A, Newsom-Davis J, et al. Autoantibodies in thymoma-associated myasthenia gravis with myositis or neuromyotonia. Arch Neurol. 2000;57(4):527-531.

6. Paik JJ, Corse AM, Mammen AL. The co-existence of myasthenia gravis in patients with myositis: a case series. Semin Arthritis Rheum. 2014;43(6):792-796.

7. Ruzhansky KM, Brannagan TH. Neuromuscular complications of hematopoietic stem cell transplantation. Muscle Nerve. 2015;52(4):480-487.

8. Schmidley JW, Galloway P. Polymyositis following autologous bone marrow transplantation in Hodgkin's disease. Neurology. 1990;40(6):1003-1004.

9. Skeie GO, Aarli JA, Gilhus NE. Titin and ryanodine receptor antibodies in myasthenia gravis. Acta Neurol Scand Suppl. 2006;183:19-23.

10. Skeie GO, Romi F, Aarli JA, Bentsen PT, Gilhus NE. Pathogenesis of myositis and myasthenia associated with titin and ryanodine receptor antibodies. Ann N Y Acad Sci. 2003;998:343-350.

11. Suzuki S, Utsugisawa K, Nagane Y, Suzuki N. Three types of striational antibodies in myasthenia gravis. Autoimmune Dis. 2011;2011:740583.

12. Suzuki S, Utsugisawa K, Yoshikawa H, et al. Autoimmune targets of heart and skeletal muscles in myasthenia gravis. Arch Neurol. 2009;66(11):1334-1338.