Clinical/Scientific Notes

O. Benveniste, MD, PhD
P. Laforet, MD
O. Dubourg, MD, PhD
S. Solly, PhD
L. Musset, PhD
S. Choquet, MD
N. Azar, MD
M. Fardeau, MD, PhD
S. Herson, MD
V. Leblond, MD, PhD*
B. Eymard, MD, PhD*

STEM CELL TRANSPLANTATION IN A PATIENT WITH LATE-ONSET NEMALINE MYOPATHY AND GAMMOPATHY

Rod bodies accumulation is the hallmark of several genetically determined congenital myopathies, generally of neonatal or childhood onset.[1] Adult forms are known as sporadic late-onset nemaline myopathies (SLONM). Since 1966, 71 patients with SLONM have been described.[2] Among them, 11 were infected by HIV[1,3] and 12 had monoclonal gammopathy,[2,4] suggesting that the association of SLONM with HIV infection or gammopathy may not be fortuitous. Plasmacytic dyscrasia with monoclonal gammopathy of undetermined significance (MGUS) can be associated with severe neuromuscular disorders, as in POEMS syndrome or AL amyloidosis, and high-dose chemotherapy with autologous stem cell transplantation has shown some efficacy in both situations.[5,6] Because of the severity and quick progression of the gammopathy-associated SLONM, we decided to propose autologous stem cell transplantation to the patient presented here.

Case report. In March 2003, a 63-year-old woman, with no family history of myopathy, presented with progressive proximal limb-girdle muscle weakness and myalgia. In February 2005, she was wheelchair-bound, could neither stand nor walk unaided, and was totally dependent for many daily life activities (table; video on the *Neurology*® Web site at www.neurology.org). Weakness was particularly severe in the proximal and axial muscles. She could swallow and breathe normally, eye and tongue movements were normal, and her speech was clear. No fasciculations were seen, and tendon reflexes and sensory perception were preserved. Three months later, she was unable to get out of bed.

Serum creatine kinase activity was 160 U/L (normal <170 U/L). Electromyography showed a non-neurogenic, myopathic pattern (short duration, small amplitude, polyphasic motor unit potentials). Muscular CT scan showed bilateral and symmetric atrophy of the posterior thigh muscles and of the gastrocnemii.

A monoclonal IgG lambda was detected by serum immunofixation (integrated peak was 2 g/L, free light chain kappa/lambda ratio was 0.11 [normal range 0.26–1.60]). Neither osteolytic nor mass lesions were found on CT or MRI of the cranium, long bones, pelvis, and spine. Bone marrow biopsy showed normal trilineage maturation with 4% of plasma cells. Tests for anti-HIV antibodies, anti-hepatitis C virus antibodies, antiacetylcholine receptor, and antinuclear antibodies were negative.

In a deltoid muscle biopsy specimen, some fibers were atrophic, scattered, and angulated, containing reddish granules on Gomori trichrome staining (figure e-1A). The distribution of type 1 and type 2 fibers was normal. No histiocytic or lymphocytic infiltration was seen, and there were no necrotizing fibers nor amyloid deposits. Direct immunostaining for HLA class I antigens was negative. Electron microscopy confirmed presence of rods in atrophic fibers (figure e-1B).

In April 2005, the patient received high-dose melphalan (140 mg/m^2) followed by autologous peripheral stem cell transplantation. Peripheral stem cells were collected at steady-state after mobilization with granulocyte colony-stimulating factor (G-CSF) alone. The only adverse effect of the procedure was transient hair loss.

She was then seen every 3 to 6 months until May 2007, for a total of 24 months. The gammopathy disappeared at the first post-transplant visit and has not reappeared. Her muscle strength improved steadily (table, video). At month 24, she could walk easily without the help of a cane (table, video). A second biopsy performed at that time in the contralateral deltoid did not show any rod (data not shown).

Discussion. The prognosis of gammopathy-associated SLONM seems poor, since out of seven patients only one remained stable during 4.5 years, one worsened during his 14 months of follow-up, and the five remaining ones died within the 5 years after symptom onset.[2] The patient reported here had a rapidly progressive form of the disease, which justified our attempt to treat her with an autologous stem cell transplantation, leading to an improvement in muscle strength.

Pathophysiology of SLONM is not known, but the favorable clinical response and the lack of further observation of the rods after the graft suggest that the

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Table Outcome of muscle functions

	Month −2	Month 0	Month 3	Month 6	Month 12	Month 18	Month 24
Myalgia	+++	+++	+	0	0	0	0
Arm abduction	45°	30°	45°	60°	ND	120°	160°
Head drop	Yes	Yes	Yes	Yes	No	No	No
Legs held outstretched at 45 deg supine	22 s	Impossible	60 s	>75 s	>75 s	>75 s	>75 s
Gait/time necessary to walk 10 meters alone	With help of someone/ND	Impossible/ND	With help of someone/ND	With 2 canes/18 s	With one cane/ND	With one cane/13 s	Alone/11 s
Standing up alone from a chair (no. of times in 1 min)	Impossible	Impossible	1	3	7	10	12

Month 0 = date of autologous peripheral stem cell transplantation.

plasma cell dyscrasia may play a part in triggering the disease. In amyloidosis there is a clear relationship between monoclonal gammopathy and AL deposits. In POEMS syndrome, the plasma cell dyscrasia has a pathogenetic role, but no clear relationship has been found between the gammopathy and the clinical manifestations, which rather appear to be due to high VEGF levels. However, both these entities improve when the plasma cell dyscrasia and the monoclonal component are eradicated.[5,6]

The risk of death from autologous stem cell transplantation, evaluated at 3% to 5% in multiple myeloma,[7] seems to be counterbalanced by its efficacy and by the poor prognosis of gammopathy-associated SLONM. Nevertheless, in AL amyloidosis, melphalan plus high dose dexamethasone was as effective and much safer than melphalan plus bone marrow transplantation.[6] These two attitudes will have to be further evaluated in SLONM.

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**Senior authors.*

From the Service de Médecine Interne 1 (O.B., S.H.), Institut de Myologie (P.L., M.F., B.E.), Laboratoire de Neuropathologie (O.D.), Laboratoire UMR S 787-Groupe Myologie (S.S.), Laboratoire d'Immunochimie (L.M.), and Service d'Hématologie (S.C., N.A., V.L.), Hôpital Pitié-Salpêtrière, Faculté de Médecine Pierre et Marie Curie, Assistance Publique Hôpitaux de Paris, France.

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Address correspondence and reprint requests to Dr. Olivier Benveniste, Service de Médecine Interne 1, Groupe Hospitalier Pitié-Salpêtrière, 47-83, Boulevard de l'Hôpital, 75651 Paris Cedex 13, France; olivier.benveniste@psl.aphp.fr

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SPORADIC LATE-ONSET NEMALINE MYOPATHY EFFECTIVELY TREATED BY MELPHALAN AND STEM CELL TRANSPLANT

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Sporadic late-onset nemaline myopathy (SLONM) is a rare, late-onset myopathy that progresses subacutely. Limb-girdle weakness and atrophy predominate the clinical picture.[1] SLONM is sporadically associated with a monoclonal gammopathy, which portends an unfavorable outcome.[1-6] We report the successful treatment of a patient with SLONM and monoclonal gammopathy with melphalan and autologous stem cell transplantation.

Clinical case. In October 2004, a 38-year-old man with no family history of myopathy started feeling fa-

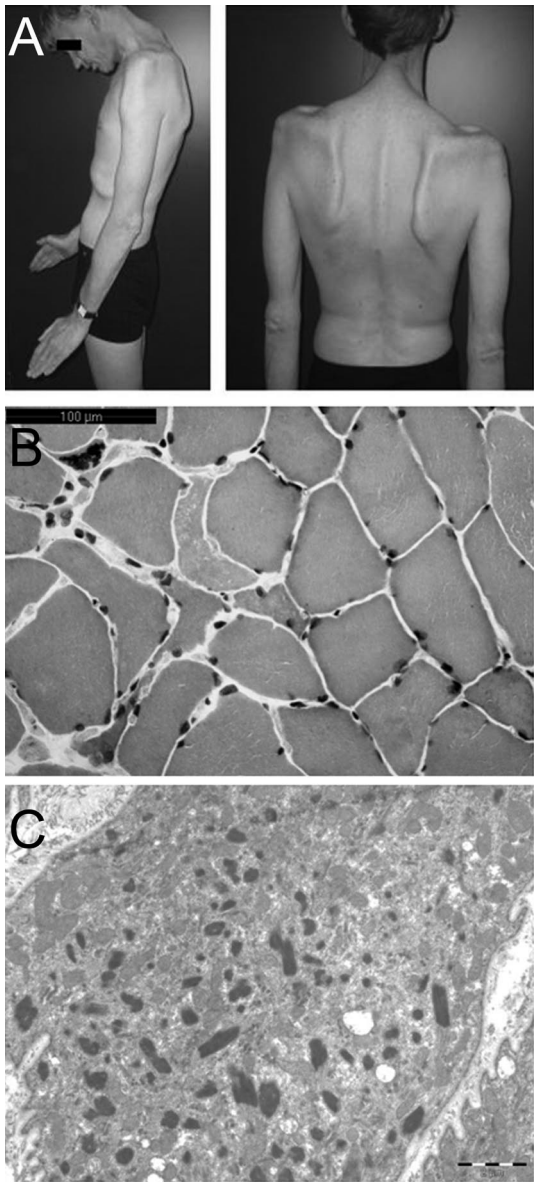
N.C. Voermans, MD*
M. Minnema, MD, PhD*
M. Lammens, MD, PhD
H.J. Schelhaas, MD, PhD
A.v.d. Kooi, MD, PhD
H.M. Lokhorst, MD, PhD
B.G. van Engelen, MD, PhD

tigued. In April 2005, he noted weakness of neck extensors, followed by weakness and atrophy of his arms and shoulders. Impairment of speech and swallowing gradually developed. In January 2006, he had mild exertional dyspnea. Laboratory investigations revealed normal CK, absence of anti-AChR antibodies, and negative viral serology, including HIV. MRI of the cervical spine was normal. Electromyography showed small, polyphasic units, with moderate spontaneous activity. Right quadriceps muscle biopsy showed atrophic fibers, but no signs of inflammation. An M-protein IgG kappa spike of 7.4 g/L was identified on serum electrophoresis and was confirmed by immunofixation. Conventional X-ray of the skeleton revealed no lytic lesions. Results of bone marrow biopsy showed an increase of monoclonal plasma cells (10–20%, almost exclusively light chain kappa positive cells), without signs of amyloidosis. Hence, monoclonal gammopathy of undetermined significance was diagnosed. The neuromuscular differential diagnosis included motor neuron disorder and inflammatory myopathy. The patient was treated with prednisone 70 mg/day for 1 month; however, dysarthria, dysphagia, and muscle weakness increased (shoulder abduction MRC2; neck extension MRC3; elbow flexion and extension MRC4) (figure).

Revision of the muscle biopsy showed not only small groups of angulated or flattened atrophic fibers, but also scattered fibers with internal nuclei, basophilic areas, or irregular ATP-ase staining and several lobulated fibers. On trichrome staining many atrophic fibers were completely filled with nemaline rods, but also larger fibers showed central or subsarcolemmal accumulations of rods, sometimes accompanied by small vacuoles. Both immunohistochemical staining with alfa-actinin antibodies (figure) and electron microscopy confirmed the abundance of these rods, classically composed of Z-band material. No amyloid was detected. Staining with kappa, lambda, and IgG antibodies revealed no abnormalities. Mutation analysis of the *NEB, TMP3,* and *ACTA1* genes was normal. SLONM associated with monoclonal gammopathy was diagnosed.

Treatment with prednisone had reduced the presence of the M-protein in serum. To further eradicate the plasma cell clone in the bone marrow, experimental treatment with one cycle of melphalan (70 mg/m^2) with peripheral stem cell collection was performed in March 2006. In May 2006 a course of high dose melphalan with autologous stem cell transplantation was performed. Two months later no M-protein was detectable in the serum, and on bone marrow examination no monoclonal plasma cells were detected. The patient attended a rehabilitation program. 15-Month clinical follow-up showed apparent improvement of muscle force and mass (shoulder abduction MRC3; neck extension MRC4; elbow flexion MRC4; elbow extension MRC5). Functional improvement was also impressive: he was able to walk upstairs and run again, speaking and swallowing were normal, and he had started working again. Cardiac and pulmonary screening were then

Figure **Clinical and histological features of patient with sporadic late-onset nemaline myopathy associated with monoclonal gammopathy**



(A) Physical examination in February 2007 revealed dysarthria, dysphagia, atrophy of temporal and frontal muscles, severe muscle weakness, and atrophy of upper and lower arms and axial muscles. Maximal anteflexion with compensatory neck flexion (left); maximal abduction (right). Fasciculations were absent and deep tendon reflexes of arms were low. (B) Quadriceps muscle biopsy revealed variation of muscle fiber diameter, with scattered atrophic fibers, some of which are quite basophilic (hematoxylin-eosin; bar = 100 μm). (C) Muscle fiber filled with rods (electron microscopy of frozen tissue; mark on bar = 2 μm).

normal. Right quadriceps muscle biopsies in August 2006 and August 2007 showed scattered atrophic, lobulated fibers. Nemaline rods were observed neither in the Gomori trichrome staining nor on electron microscopy.

Discussion. SLONM is an atypical disorder that normally presents after age 40 and progresses subacutely. Limb-girdle weakness and atrophy predominate the clinical picture, but distal weakness, head drop, respiratory insufficiency, and dysphagia can also occur.[1] Although fasciculations and hyperreflexia are absent, patients may be misdiagnosed with motor neuron disease. Recognition of nemaline rods on trichrome staining is crucial. This can be confirmed by immunohistochemical staining with alfa-actinin antibodies of the muscle biopsy.

Presence of monoclonal gammopathy in SLONM portends an unfavorable outcome: the majority of these patients die within 1 to 5 years of respiratory failure, despite immunosuppressive treatment.[1] Presence of a monoclonal protein at the sarcolemma and responsiveness to immunosuppressive treatment are suggestive of an autoimmune origin.[1,4,5] In contrast to these previously reported cases, this patient showed significant improvement of muscle strength and function that was accompanied by a remarkable improvement of the muscle histology in response to treatment. Treatment with high dose melphalan and stem cell transplantation has a relatively low mortality when cardiac or visceral involvement is absent.[7] Since the natural course of SLONM with monoclonal gammopathy is devastating, this report is imperative and calls for further study. Finally, it stresses the importance of recognition of this remarkable mimic of motor neuron disease.

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**These authors contributed equally to this article.*

From the Neuromuscular Centre Nijmegen (N.C.V., M.L., H.J.S., B.G.v.E.), Department of Neurology, and Department of Pathology (M.L.), Radboud University Nijmegen Medical Centre; Department of Haematology (M.M., H.M.L.), University Medical Centre Utrecht; and Department of Neurology (A.v.d.K.), Amsterdam Medical Centre, the Netherlands.

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Address correspondence and reprint requests to Dr. B.G. van Engelen, Neuromuscular Centre Nijmegen, Department of Neurology, 935, Radboud University Nijmegen Medical Centre, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands; b.vanengelen@neuro.umcn.nl

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