Autologous stem cell transplantation in a patient with sporadic late-onset nemaline myopathy and monoclonal gammopathy: First Moroccan experience

Autogreffe de cellules souches hématopoïétiques pour une myopathie à bâtonnets de survenue tardive associée à une gammapathie monoclonale : première expérience marocaine

Introduction

Sporadic late-onset nemaline myopathy (SLONM) is a very rare disorder. It was first described in 1966 by Engel in two patients [1] and by Engel and Resnick in another patient [2]. The disease typically appears after the fourth decade of life and progresses subacutely. Limb-girdle and axial weakness and atrophy predominate the clinical picture, but distal weakness, head drop, respiratory insufficiency, and dysphagia can also occur. Patients may be suspected to have motor neuron disease because of the rapid course and severe atrophy. Serum creatine kinase (CK) level usually is normal or slightly raised. Electromyography (EMG) examination shows myopathic features associated with fibrillation potentials. The diagnosis is readily confirmed by biopsy of a clinically affected muscle. Recognition of nemaline rods on trichrome and α-actinin staining or electron microscopy is crucial. Clusters of rods, often filled atrophic fibers, are the pathological hallmark of this disease [3].

In SLONM, the proportion of muscle fibers affected by rod formation and the number of rods per cell are known to vary within muscles in different patients as well as in the same patients. Various intrasarcoplasmic changes, including basophilic, small vacuoles, granular degeneration, small and more punctuate nemaline structures (fewer typical rod-shaped nemaline bodies) with variable degrees of myofibril affectation are distinctive features of SLONM [3].

However, nemaline rods have been described as an incidental and minor feature in several neuromuscular diseases. In such situations, the clinical presentation and examination findings are usually consistent with the primary disease process [4]. The pathogenic mechanism underlying this non-hereditary form of nemaline myopathy remains unknown. However, because of the frequent association of SLONM with human immunodeficiency virus (HIV) infection and monoclonal gammopathy of unknown significance (MGUS), an acquired immune dysregulation has been suggested [3,5]. In some cases of SLONM-MGUS, deposits of circulating monoclonal immunoglobulin was detected on the surface of the myofibers [6,7]. These deposits rather than the nemaline bodies may have myotoxic effects on skeletal muscle [8]. The association of MGUS with SLONM portends an unfavorable outcome: the majority of these patients die within 1 to 5 years of respiratory failure [3].

Some SLONM-MGUS patients respond to high-dose melphalan (HDM) followed by autologous stem cell transplantation (ASCT) or to intravenous immunoglobulins (IVIGs) [9–12].

Most recently, Voermans et al. reported a series of 8 patients with SLONM-MGUS. This retrospective study on the long-term follow-up shows that the probability of survival, muscle strength, and functional capacities of these patients improve after treatment with HDM followed by ASCT (class IV evidence) [13].

We report through this work, the case of a patient with SLONM-MGUS whose disease evolved gradually since the age of 40. HDM Followed by ASCT was administered to the patient at the age of 45. A significant clinical response and hematologic very good partial response (VGPR) were recorded at the 5-month post-transplantation. Unfortunately, he then died because of Salmonella typhi septicemia.

Case report

A 40-year-old man showed progressive painless weakness of proximal limb muscles. At the age of 44 years, he could not stand or walk and was unable to lift his arms over his head. He was bedridden and experienced occasional difficulty in swallowing solid foods although he did not need assistance with nasogastric tube. He presented also with a respiratory weakness. He had a past medical history of recurrent biliary pancreatitis. There was no family history of neuromuscular disease.

At neurological examination, there was a severe weakness affecting proximal limb muscles (0-2/5), trunk flexors (0/5), neck flexors (2+) and extensors (3/5). He had also mild bifacial weakness and distal weakness in both upper (4+/5) and lower
limbs (3/5) according to the Medical Research Council (MRC) scale (table I). Deep tendon reflexes were absent and no fasciculations were observed. His sensory perception was preserved. Eye movements were normal and he had no dysarthria. Serum CK activity was 143 U/L (normal < 170 U/L). EMG showed a myopathic pattern as well as fibrillation potentials in affected muscles. Nerve conduction studies were normal. Respiratory function exploration revealed a restrictive pattern with a reduced vital capacity of 2.13 L (47.7% of predicted). Echocardiography revealed an asymptomatic left ventricular systolic dysfunction with a reduced ejection fraction at 42%. Neither dilated nor hypertrophic cardiomyopathy were observed.

A low level of monoclonal IgG kappa protein (0.4 g/L) was detected by serum immunofixation. X-ray examination revealed no osteolytic lesions, bone marrow aspiration was normal, and there was therefore no evidence in favor of myeloma. HIV antibodies and inflammatory markers were negative.

Biopsy of the right vastus externus muscle showed marked variation in muscle fibre size with atrophic and hypertrophic fibres, rounded fibres and increased number of fibres with internal nuclei. Other findings were cytoplasmic basophilia in some fibres and increased number of vacuoles. There were neither inflammatory changes nor amyloid deposits. Electron microscopic examination revealed muscle fibres with thickened 2-bands associated with large numbers of short nemaline rods and disorganized myofibrils. The percentage of muscle fibres with nemaline rods was 20% (figure 1). SLONM-MGUS was diagnosed.

At the age of 45, a course of HDM (200 mg/m²) followed by ASCT was performed. Peripheral stem cells were collected at steady-state after mobilization with granulocyte colony-stimulating factor (G-CSF) alone. The number of transplanted stem cells was $5 \times 10^6$ CD34⁺ cells per kilogram body weight. The course during the first 3 weeks after ASCT was marked by the occurrence of an acute pancreatitis managed by medical

### Table I

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Month 0</th>
<th>Month 3</th>
<th>Month 5</th>
</tr>
</thead>
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<tr>
<td>Trapezius</td>
<td>2⁻</td>
<td>2⁻</td>
<td>2⁻</td>
</tr>
<tr>
<td>Neck flexors</td>
<td>2+</td>
<td>2+</td>
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</tr>
<tr>
<td>Neck extensors</td>
<td>3</td>
<td>3</td>
<td>3⁺</td>
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<tr>
<td>Passage from dd to sd</td>
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<td>np</td>
<td>np</td>
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<tr>
<td>Deltoid</td>
<td>2⁻</td>
<td>2⁻</td>
<td>4</td>
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<td>Arm abduction</td>
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<td>40°</td>
<td>90°</td>
</tr>
<tr>
<td>Coracobrachialis</td>
<td>2⁻</td>
<td>2⁻</td>
<td>4⁺</td>
</tr>
<tr>
<td>Biceps brachii</td>
<td>2⁻</td>
<td>2⁻</td>
<td></td>
</tr>
<tr>
<td>Triceps</td>
<td>2⁻</td>
<td>2⁻</td>
<td>4⁺</td>
</tr>
<tr>
<td>Muscles of hand/wrist</td>
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<tr>
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<td></td>
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<tr>
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</tr>
<tr>
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<td>4⁺</td>
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<tr>
<td>M-protein</td>
<td>0.4 g/L</td>
<td>nd</td>
<td>Detectable but unquantifiable</td>
</tr>
</tbody>
</table>

Month 0: date of autologous stem cell transplantation; Strength measured according to MRC scale; dd: dorsal decubitus; sd: sit down; np: not possible; nd: not done.
treatment. One month and a half after ASCT, the patient had returned home and started motor rehabilitation program. At 3 months post-transplantation, objective assessment of muscle strength remained unchanged although, the patient noted subjective improvement of heaviness in the limbs. At 5 months post-transplantation, there was a marked improvement in muscle testing of the upper limbs (MRC score 4 to 5/5 for proximal muscles), and a slight improvement of the testing of lower limb muscles and neck extensors; the other axial muscles remained stable (Table I). This improvement in muscular strength has allowed the patient to regain some of his functional autonomy especially in the use of his upper limbs (self-feeding, toiletries and shaving the face). Serum immunofixation was made (at the 5th month post-transplantation) and showed VGPR (monoclonal protein was detectable but not quantifiable). At the end of the 5th month post-ASCT, the patient was admitted for a severe Salmonella typhi septicemia. Medical history found a recent diarrhea among relatives. Unfortunately, the patient was seen late, a week after the onset of sepsis symptoms. Despite administration of intensive antibiotherapy and hospitalization in the ICU, worsening of his clinical condition occurred and the patient died a few days later.

**Discussion**

Immunosuppressive therapy with either prednisone alone or in combination with a steroid-sparing immunosuppressant agent in HIV negative SLONM/MGUS is unsuccessful [3]. Concomitant MGUS leads to a poor prognosis, 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 6 years after symptom onset [3]. However, two patients with non-HIV SLONM/MGUS were reported to be responsive to IVIGs alone or in combination with immunosuppressant agents [12].

Most recently, Voermans et al. reported a series of 8 patients with SLONM-MGUS, from which 7 out of 8 had at least a transient response to HDM-ASCT. Therefore, this study provided a class IV evidence of the positive effect of HDM-ASCT for the probability of survival and function improvement even in long-term follow-up. Factors that may portend an unfavorable outcome are a long disease course before the hematologic treatment and a poor hematologic response. Age at onset, level and type of M-protein (kappa vs. lambda), and severity of muscle weakness were not associated with a specific outcome [13].

Despite the long duration of the disease before ASCT, our patient showed a significant improvement in motor strength (especially in upper limbs) and functional abilities five months after transplantation in parallel to VGPR. However, infections are still a major cause of mortality in ASCT patients, increased susceptibility to infectious agents being an inevitable consequence of the associated immunosuppression. Unfortunately, our patient was seen late and intensive care failed to control sepsis-related complications.

In addition to the distinctive features of SLONM-MGUS in our case, an asymptomatic and isolated left ventricular systolic dysfunction was also disclosed at the end of the 5th year of progression of the disease, suggesting a probable cardiomyopathy. Cardiomyopathy in SLONM-MGUS was reported only once in the literature [14].
In this recent observation, Sarullo et al. reported the case of a 37-year-old male patient with SLONM-MGUS who developed a dilated cardiomyopathy with severe congestive heart failure. Presumably, cardiac involvement is a very rare event in SLONM-MGUS. This scarcity may be explained by the assumption that the cardiomyopathy may be mainly seen in the advanced stages of the disease, when motor impairment and respiratory failure are important. Therefore, the absence of cardiomyopathy in the two large series in the literature relating to SLONM-MGUS [3,13] may be explained by the under-representation of patients at advanced stages of the disease (only 1/7 patients reached 5 years of evolution in the Chahin’ series; and only 2/8 patients reached 5 years or more in Voermans’ one). Finally, in spite of the short duration of post-ASCT monitoring not exceeding six months because of patient’s death, our observation adds to the literature another case of responsive SLONM-MGUS to HDM and ASCT.

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References


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