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### **► To cite this version:**

Diana Maria Chitimus, Édouard Berling, Laurent Garderet, Nadia Venturelli, Edoardo Malfatti, et al.. Systemic light chain amyloidosis myopathy responsive to daratumumab monotherapy. *European Journal of Neurology*, 2023, 30 (3), pp.745-748. <10.1111/ene.15640>. <hal-04122462>

**HAL Id: hal-04122462**

**<https://hal.science/hal-04122462v1>**

Submitted on 4 Jul 2023

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## SHORT COMMUNICATION

# Systemic light chain amyloidosis myopathy responsive to daratumumab monotherapy

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## Abstract

**Background and purpose:** Amyloid myopathy is a rare and severe manifestation of systemic light chain (AL) amyloidosis. Early diagnosis and staging are mandatory for optimal therapy, given the rapid progression of muscle weakness. Despite the efficacy of bortezomib-based treatment regimens, there is a lack of therapeutic alternatives in non-responsive patients.

**Method:** The case report of a patient with systemic AL amyloidosis myopathy treated with daratumumab is presented.

**Results:** A 70-year-old man displayed severe proximal muscle weakness which had developed over a 10-month period. Blood tests revealed an immunoglobulin A lambda monoclonal gammopathy, whilst muscle biopsy showed amyloid deposits within the arteriolar walls, confirming the diagnosis of amyloid myopathy associated with AL amyloidosis. Initial treatment with a bortezomib-based regimen showed no clinical or hematological improvement. After switching to daratumumab monotherapy, our patient achieved a favorable evolution with respect to functional muscle scoring and a complete hematological response.

**Conclusion:** To our knowledge, this is the first case report of an amyloid myopathy showing a remarkable clinical improvement in response to daratumumab monotherapy. It thereby highlights the potential of daratumumab as a monotherapeutic approach to the treatment of amyloid myopathy complicating AL amyloidosis.

## KEYWORDS

amyloid myopathy, daratumumab, light chain amyloidosis, systemic AL amyloidosis

## INTRODUCTION

Immunoglobulin light chain (AL) amyloidosis represents the most common type of systemic amyloidosis. It is characterized by the misfolding of immunoglobulin light chains synthesized by plasma cell clones, leading to insoluble fibrillar aggregates which infiltrate multiple organs [1].

Skeletal muscle involvement is rare, occurring in no more than 1.5% of cases [2, 3]. The majority of patients present a severe progressive symmetrical proximal weakness, whilst also displaying cardiac involvement. Standard treatment employs therapies targeting plasma cells, especially bortezomib-based regimens [4]. The prognosis of amyloid myopathy is poor, with a median overall survival of 32 months, as

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reported in a recent study of 51 patients [5]. The human immunoglobulin G kappa (IgG-κ) monoclonal antibody daratumumab, which targets the CD38 glycoprotein of plasma cells, has proved to be highly efficient in treating AL amyloidosis [6]. However, to our knowledge there is no consensus concerning its impact on amyloid myopathy.

## METHOD

The clinical and histopathological features of a male patient diagnosed with AL amyloidosis myopathy who responded favorably to daratumumab monotherapy are described.

In accordance with French legislation, the study was approved by the local ethics committee and by the French data protection authority (Commission Nationale de l'Informatique et des Libertés). Informed consent was obtained from the patient involved in the study.

## RESULTS

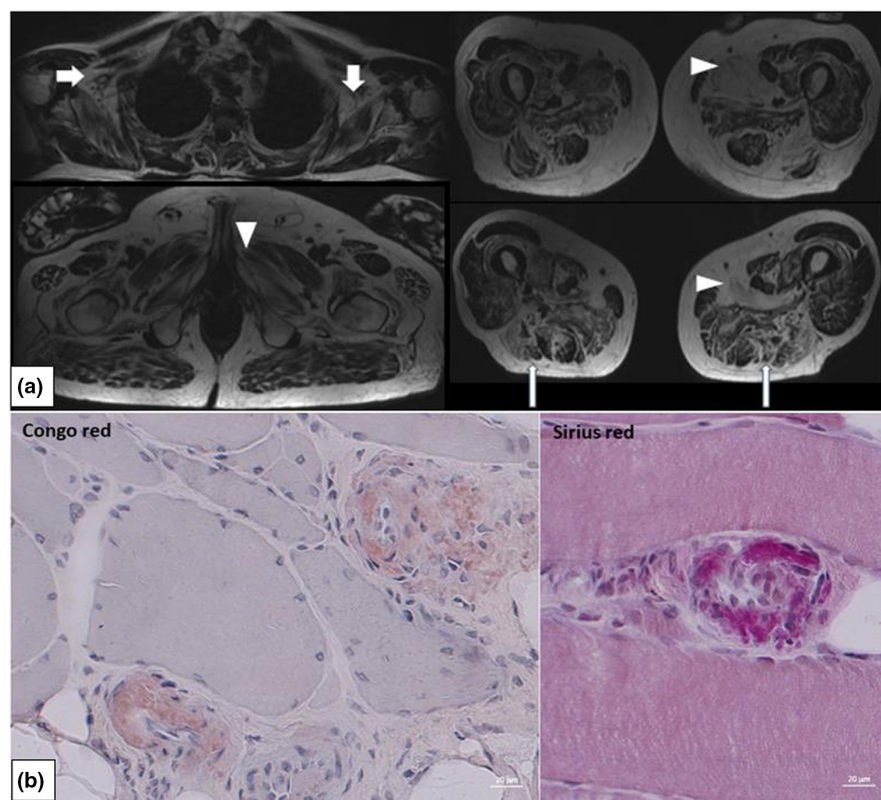
A 70-year-old man was admitted to hospital for progressive muscle weakness which had developed over a 10-month period, necessitating walking assistance. A sudden weight loss of 14 kg was also reported. There was no record of previous motor disabilities in childhood or adulthood. The medical history included essential tremor, hypothyroidism, mitral valvuloplasty, atrial fibrillation and high blood pressure controlled by pharmacological treatment. No consanguinity or significant family history was present.

The neurological examination revealed symmetrical proximal muscle weakness: 3/5 in the lower limbs versus 4/5 in the upper limbs and a moderate axial weakness of 4/5, quantified on the Medical Research Council scale. There was no respiratory muscle involvement or dysphagia. Electromyography revealed a proximal myopathic pattern.

Whole body muscle magnetic resonance imaging (MRI) showed marked symmetrical atrophy of the biceps femoris and asymmetrical atrophy of the hip adductors, particularly in the left adductor longus (Figure 1a). Axial muscles and scapular girdle muscles displayed a less severe pattern of atrophy.

Complete blood cell count, serum creatinine, urea and hepatic markers were within the normal ranges, whilst serum creatine kinase levels were slightly elevated (600 U/l). An extensive panel of antibodies was performed, including myositis-specific autoantibodies and anti-HMGCR antibodies, with negative results. Serum immunoglobulin analysis showed an increased IgA value (4.4 g/l), with protein electrophoresis and immunofixation further confirming the monoclonal IgA peak. The serum lambda free light chain concentration was increased (214 mg/l) whilst the serum kappa free light chain concentration was within the normal range; hence the serum kappa/lambda ratio was drastically reduced (0.07) and the difference between involved and uninvolved serum free light chains was increased (199 mg/l). The plasma cell count in the bone marrow revealed a CD 38/138+ plasmacyte population of 8%. No proteinuria was detected and the Bence Jones test was negative.

Cardiac biomarkers showed increased levels of hsTnT (high sensitivity cardiac troponin T; 280 ng/l) and NT-proBNP (N-terminal pro-hormone of brain natriuretic peptide; 1600 ng/l). Cardiac echography



**FIGURE 1** Explorations findings. (a) Whole-body muscle MRI. Fat imaging of the T2 Dixon axial sequence showing fatty infiltrations with bilateral, symmetrical amyotrophy, predominating in the lower limbs, more severe in the adductors (Mercuri 4), particularly in the left adductor longus (arrow heads), the hamstrings (long arrows), as well as in the medial and lateral soleus and gastrocnemius. The upper limb involvement mainly concerns the shoulder girdle (short arrows) and in particular the rotator cuff (Mercuri 3). The paraspinal muscles are moderately to severely affected (not shown). (b) Muscle biopsy. Congo red staining of a frozen muscle section (left) and Sirius red staining of a paraffin section (right), showing the presence of red material corresponding to amyloid deposits within the endomysial vessels. Note the variation in fiber size and the multiple nuclear internalization in the left panel.

revealed a slightly hypertrophied but non-dilated left ventricle, with good overall contractile function (left ventricular ejection fraction 59%). The cardiac MRI also suggested amyloid infiltration. No other organ involvement was found.

The deltoid muscle biopsy confirmed the presence of amyloid deposits within the walls of small arteries, using both Congo red and Sirius red staining (Figure 1b). No rods were present on the Gomori trichrome staining. Given the overall findings, the diagnosis of AL amyloidosis Mayo stage IIIA was established.

A 6-month cycle of therapy with cyclophosphamide, bortezomib and dexamethasone (CyBorD) was initiated, with unsatisfying results, however, which led to cessation of the first-line treatment. Second-line daratumumab monotherapy was then started. The patient received 1.8 g of daratumumab subcutaneously once a week for the first 2 months, followed by every 2 weeks for 4 months and then by monthly administration once a month for 18 months, until the present day. This resulted in a favorable evolution, with regard to both the functional state of the patient and the normalization of hematological parameters (Figure 2).

Two years after the diagnosis and the aforementioned treatment, the patient achieved a complete hematological response, according to current criteria [7].

Clinically, the patient reported an important functional improvement. Namely, the range of active movement for abduction and flexion of the arms increased to 170° on both sides (vs. 100° at the first examination). The manual muscle test showed an improvement in the neck muscles (5/5) and in the bilateral proximal deltoid muscles and hamstring muscles, with a score of 4/5 on both sides. The upper limb Barré test progressed to 2 min 30s (vs. 1 min 37s at the first examination). The serum creatine kinase levels decreased (156 U/l).

## DISCUSSION

The diagnosis of late-onset proximal myopathy is strenuous, given the plethora of potential genetic and acquired etiologies. Amongst

the acquired myopathies, amyloid myopathy is particularly challenging, since the muscular signs and symptoms can develop for up to 10–20 months before the diagnosis is made [5]. The discovery of an abnormal circulating monoclonal immunoglobulin light chain raised the suspicion of AL amyloidosis in our patient.

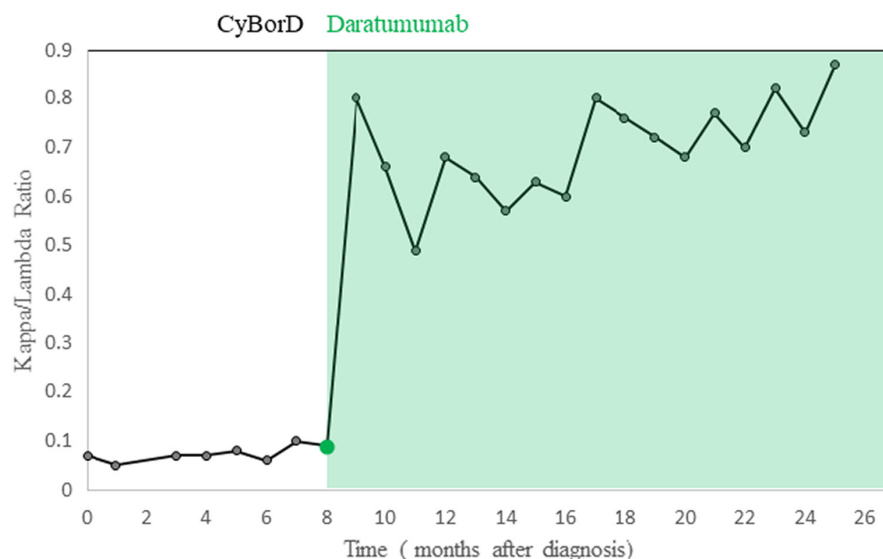
From one perspective, systemic AL amyloidosis has an increased prevalence in individuals of over 65 years, approximately 55% of whom are men [8]. A similar disease evolution is seen in sporadic late-onset nemaline myopathy, which frequently appears as a rapidly progressive weakness in the axial and proximal limb muscles. An association with monoclonal gammopathy of undetermined significance may be present in both conditions. A recently published case report described the coexistence of sporadic late-onset nemaline myopathy and amyloid myopathy, raising the question of a possible correlation between the two [9]. In our case, muscle biopsy did not reveal the presence of rods.

Muchtar et al. [5] identified a few common features to skeletal muscle involvement in AL amyloidosis, in an observational study of a cohort of 51 patients: first, the strong association of amyloid myopathy with lambda light chain dysproteinemia; secondly, the muscle biopsy findings, characterized by rare necrotic and regenerating fibers and interstitial amyloid deposits in intramuscular blood vessels, which are consistent with previous reports [10]; lastly, the shared clinical aspects, such as proximal muscle weakness, dysphagia, macroglossia and, less frequently, muscular pseudohypertrophy or respiratory distress [5, 11, 12]. In addition, cardiac troponin T elevation, without evidence of cardiac involvement, might provide a clue enabling early diagnosis [2, 5].

In our case, many of the assembly of clinical and non-clinical elements reported before were found. However, a distinguishing element was the identification of IgA as the M protein, instead of the more common IgG [5].

Once diagnosed, patients with systemic AL amyloidosis are subjected to a risk stratifying procedure, which usually determines the optimal therapeutic approach [1]. The revised Mayo staging criteria include both cardiac and hematological biomarkers, thereby improving the risk stratification for the patients and consequently enabling a more personalized treatment [13]. The prognosis of AL amyloidosis

**FIGURE 2** Variation of the serum kappa/lambda chain ratio with time over the treatment period. A drastic improvement followed the introduction of daratumumab. CyBorD, cyclophosphamide, bortezomib and dexamethasone



is dictated by the cardiac involvement; hence for each Mayo stage there is a median duration of survival. Our patient was classified as Mayo stage IIIA, which corresponds to a mean survival of 12 months post diagnosis. As an intermediate-risk patient, considered ineligible for autologous stem cell transplantation, the first-line treatment option was the CyBorD regimen. Even though the remission rate of this regimen is reportedly high, with up to 66% of stage II and III patients responding favorably, in our case it was not efficient [4]. Switching to anti-CD38 monoclonal antibody monotherapy resulted in a positive outcome, with complete hematological remission and normalization of the serum kappa/lambda chain ratio in <1 year of monthly administration (Figure 2). Although the introduction of daratumumab monotherapy in the relapse setting has generated positive reviews in the latest publications, its impact on the specific involvement of skeletal muscles has not been clearly described [6]. In terms of treatment rentability, in France, a rough estimate rendered a 10-fold increase in costs for the first two cycles, compared to CyBorD therapy [14].

To our knowledge, this is the first case report of amyloid myopathy in systemic AL amyloidosis responding favorably to daratumumab monotherapy. The cessation of myopathy progression and the clinical improvement positively correlated with the complete hematological response. Whilst there is no consensus regarding the optimal period of treatment with daratumumab, one may consider administering the quadruplet CyBorD plus daratumumab until complete remission is obtained [15].

## AUTHOR CONTRIBUTIONS

Diana Maria Chitimus: Conceptualization, writing of the original draft (leading author). Edouard Berling: Writing, reviewing and editing, supervision. Laurent Garderet: Resources, investigation, reviewing and editing. Nadia Venturelli: Resources, investigation, reviewing and editing. François Jérôme Authier: Resources, investigation. Edoardo Malfatti: Resources, investigation, reviewing and editing. Guillaume Nicolas: Investigation, supervision. Pascal Laforêt: Investigation, supervision. Claire Lefeuvre: Investigation, writing, reviewing and editing, supervision.

## CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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**How to cite this article:** Chitimus DM, Berling E, Garderet L, et al. Systemic light chain amyloidosis myopathy responsive to daratumumab monotherapy. *Eur J Neurol*. 2023;30:745-748. doi:10.1111/ene.15640