

A Case of Lambda AL Type Skeletal Amyloidosis with Vascular Myopathy Achieved Clinical Response after Autologous Stem Cell Transplant

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Abstract

Amyloidosis involving the vascular musculoskeletal system is rare and currently, there is no standard treatment protocol for the treatment of skeletal muscle AL amyloidosis associated with vascular myopathies. Furthermore, the data on the efficacy and safety of autologous stem cell transplant is unclear. In this rare case, a biopsy-proven diagnosis of AL type amyloidosis with an unusual presentation of proximal muscle weakness significantly improved with high dose melphalan followed by autologous stem cell transplantation. The patient achieved and maintained remission for a year post-transplant.

Keywords: Skeletal Muscle; Amyloidosis; Vascular Myopathy; Autologous Stem Cell Transplant

List of abbreviations: AL: Light-Chain; CyBorD: Cytoxan, Velcade, and Dexamethasone; Auto-SCT: Autologous Stem Cell Transplant; HDM: High-Dose Melphalan, MM: Multiple Myeloma, SPEP: Serum Protein Electrophoresis; IPEP: Immuno-Protein Electrophoresis; K/L: Kappa Over Lambda; EMG: Electromyogram; LC-MS/MS: Liquid Chromatography-tandem Mass Spectrometry; EKG: Electrocardiogram; MRI: Magnetic Resonance Imaging; BNP: Brain Natriuretic Peptide; IFE: Immunofixation Electrophoresis

Introduction

Amyloidosis and its types are a group of rare protein-misfolding disorders that involve tissue deposition of protein fibrils. These protein deposits accumulate, often in the extracellular tissue, disrupting the function of the surrounding tissue and organ. This leads to debilitating symptoms, usually at an advanced stage. Systemic light chain (AL) amyloidosis is the most common of the amyloidosis disorders [1], and the AL type is the most serious form [2]. Other conditions, like wild-type transthyretin cardiac amyloidosis (ATTRwt), are being more frequently diagnosed [1]. These disorders can be very difficult to catch, and this often leads to a delayed diagnosis in the clinic [3]. Diagnosis and typing of amyloidosis involves laser capture, mass spectrometry, and histological tissue sections from biopsies [1] diagnostics that are not as commonly considered by physicians at first. Furthermore, amyloidosis is often initially asymptomatic, and when symptoms do surface, they may collectively appear to be other more common health issues. These are reasons as to why it is sometimes missed in the clinical presentation. Since early diagnosis is a key to better outcomes, this results in disease progression-not to mention a more difficult time treating it-before it is finally discovered in a patient.

This case report discusses a patient with skeletal muscle AL amyloidosis with vascular myopathies and minimal other-organ involvement. This is even rarer, as cardiac protein fibril deposition is a very frequent feature of amyloidosis [4]. There are no reported statistics on the percentage of AL amyloidosis patients who suffer from amyloid pathologies involving skeletal muscle and vascular tissue. While systemic amyloidosis does typically result in skeletal muscle amyloid deposition, this is typically silent [5] specifically, it is rare to find muscle weakness in the clinical presentation. Even more, it is even rarer to find vasculitis or vascular myopathies as well. Deposition of the protein fibrils does not usually affect the vasculature of the skeletal muscle, but rather only the muscle fibers themselves. As for treatment options, one of the key elements of treating amyloidosis is aggressive management that involves the triple therapy, CyBorD (Cytoxan, Velcade, and dexamethasone). There also seems to be promising strategies on the horizon as the therapeutic landscape for amyloidosis widens to include RNA inhibitors, fibril formation stabilizers, and even immunotherapeutic targeting of the amyloid deposits [1]. However, there is

no protocol or standard of treatment of lambda AL amyloidosis specifically involving vascular myopathies. Further, the data for autologous stem cell transplant (auto-SCT) and its effectiveness is unclear. In the recent literature on AL amyloidosis, there are a limited number of reports that have discussed the use of auto-SCT as a viable treatment option in the era of novel immune therapy in plasma cell disorders. One such study showed that induction with bortezomib may be associated with longer survival than other strategies, speculating that induction therapies could be a selection mechanism; if patients could handle the bortezomib chemotherapy; they were resilient enough to endure the following high-dose melphalan (HDM) and auto-SCT [6].

The objective of this case report is two-fold: (1) to bring awareness to the importance of considering amyloidosis and its types in a differential diagnosis and (2) to shine a spotlight on the efficacy of auto-SCT in cases of amyloidosis where myopathies are present. While amyloidosis of the skeletal muscle with vascular myopathies and minimal involvement of other organs is a rare case to see, this case should encourage the investigation of auto-SCT as a potential avenue of treatment for future amyloidosis patients.

Methodology

A patient's medical history was examined and summarized in order to elucidate the chronology of the amyloidosis diagnosis, treatment, and prognosis. A patient consent form was signed by the patient. A skeletal muscle biopsy was performed in the thigh. Liquid chromatography-tandem mass spectrometry (LC-MS/MS) was performed on tissue fragments microdissected from Congo red positive areas of the biopsy specimen using a previously published method [7]. For purposes of clarity, the rest of the diagnostic methods are explained within the chronology of the case below.

Clinical Case

A 63-year old female presented with a family history of her mother passing due to multiple myeloma (MM) at age 84. Two years prior, the patient had an invasive lobular carcinoma (grade 1, Bloom-Richardson 5/9), with an estrogen positive, progesterone positive, HER2/neu negative disease. She had a mastectomy in 2016, and now there is no current evidence of the disease. In 2019, the patient presented with muscle weakness and fatigue in the legs that had been worsening over the previous two years. The patient did not have any myeloma defining features. She had normal renal function and creatinine clearance and no hypercalcemia or anemia on bloodwork. A bone survey revealed no sclerotic bone lesions. A bone marrow biopsy was performed, which showed 1% lambda restricted plasma cells. Also, a Congo red stain turned out negative for amyloid deposition in the bone marrow.

Serum Protein Electrophoresis (SPEP) did not identify monoclonal proteins, but Immuno-Protein Electrophoresis (IPEP) did detect a faint amount of IgG kappa with an IgG level of 574. This did not correlate with the bone marrow clonal plasma cell results, which means that the patient possibly had 2 different clones. A 24-hour urine protein test was within normal limits without proteinuria. Urine immunofixation electrophoresis (IFE) was normal. A serum free light chain test showed that the patient had a kappa level of 0.64 and a lambda level of 6.9, with a kappa over lambda (K/L) light chain ratio of 0.10. All these findings indicated monoclonal gammopathy of unknown significance. The patient was evaluated for muscle weakness with an electromyogram (EMG), the results of which ruled out neurological pathology. A skeletal muscle biopsy was performed, which confirmed that she had skeletal muscle amyloidosis of the AL type. The Congo red staining can be seen in Figure 1. A Congo red stain was performed on paraffin sections of the specimen, which showed Congo red-positive amyloid deposits present. Peptides were extracted from Congo red-positive areas of the specimen and then mass spectrometry, specifically LC-MS/MS, was performed on these peptides. The results of the mass spectrometry, seen in Figure 2, confirmed it was IgG lambda AL amyloidosis.

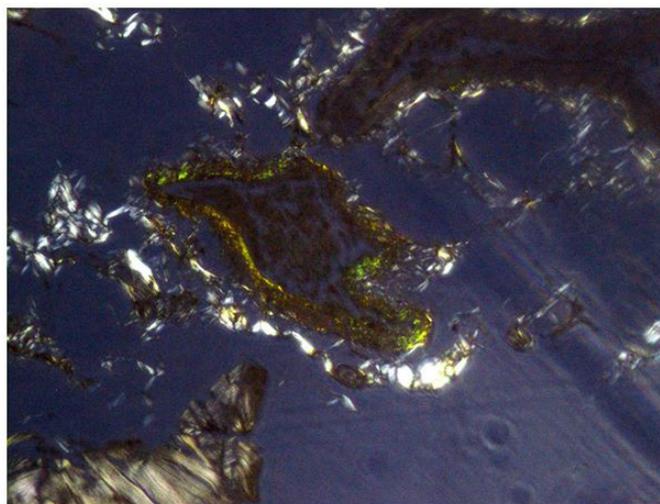


Figure 1: A Congo red stain was performed on paraffin sections of the specimen. Congo red-positive amyloid deposits are present. Liquid chromatography tandem mass spectrometry (LC MS/MS) was performed on peptides extracted from Congo red-positive, microdissected areas of the paraffin-embedded specimen. LC-MS/MS detected a peptide profile consisted with AL (lambda)-type amyloid deposition

#	Visible?	Starred?	Bio View: Identified Proteins (104) Including 5 Decoys	Accession Number	Molecular Weight	Protein Grouping Ambiguity	Probability Legend:	
							over 95%	80% to 94%
							Sample 1	Sample 2
1	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	★ Apolipoprotein A-IV	APOA4_HU...	45 kDa		105	110
2	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	★ Apolipoprotein E	APOE_HUM...	36 kDa		65	64
3	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	★ Ig lambda-2 chain C regions	LAC2_HUM...	11 kDa	★	48	48
4	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	★ Apolipoprotein A-I	APOA1_HU...	31 kDa		44	40
5	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	★ Ig lambda chain V-I region VOR	LV101_HU...	12 kDa		31	24

Nb. The significance of finding only lambda LV-1 is that it is tantamount to demonstrating clonality and implies that the amyloid must arise from a clonal lymphocyte/plasma cell population. (Dasari S, Theis JD, Vrana JA, Meureta OM, Quint PS, et al. (2015) Proteomic detection of immunoglobulin light chain variable region peptides from amyloidosis patient biopsies. *J Proteome Res* 14 (4): 1957-67. doi: 10.1021/acs.jproteome.5b00015.)

Figure 2: Protein identification profile of amyloid microdissected from the paraffin embedded muscle biopsy specimen and analyzed by LC-MS/MS. Amyloid-related proteins are marked with stars and displayed at the top of the list. The numbers displayed in the boxes in the vertical columns represent the total number of spectra matched to the listed protein. The colors of the boxes represent the probability that the spectra represent the identified protein (only spectra with 95% probability of a match to an identified protein [green boxes] are considered for diagnostic interpretation). The specimen contains Apolipoprotein AIV and apolipoprotein E, two proteins deposited with amyloids of all types. In addition there were abundant spectra corresponding to the lambda light chain constant region and the lambda variable region family 1

Besides the skeletal muscle vessels, there was no clinical evidence of involvement of organs. Upon further evaluation, findings did indeed show very minimal involvement of amyloid deposits in other organs. Electrocardiogram (EKG) results showed low voltage with mild diastolic dysfunction on the echocardiogram. Unfortunately, cardiac magnetic resonance imaging (MRI) was not conducted due to issues with insurance approval. However, Mayo Clinic Cardiac Staging resulted in AL amyloidosis Stage 1: troponin was less than 0.05 ng/mL, brain natriuretic peptide (BNP) was less than 25 pg/mL [8]. Finally, there was no Congo red positive amyloidosis in the bone marrow, kidneys, gastrointestinal tract, liver, or in the fat pad-confirming minimal other-organ involvement.

To summarize the clinical case, the patient had peripheral IgG lambda light chain vascular myopathy and her hematological markers showed slight free lambda light chain. The patient had minimal plasma dyscrasia and possibly has two different clones as the bone marrow biopsy plasma cells showed 1% lambda-restricted clones too. She was thus diagnosed with lambda light chain amyloidosis with vascular myopathy.

To treat the patient, she was started on steroids for her vascular myopathy. She was also started on CyBORd (Cytoxan, velcade, and dexamethasone) and completed four cycles. After these four cycles, her K/L ratio successfully increased to normal limits and the free serum light chain values normalized. Urine IFE remained normal throughout. Since she had minimal hematologic involvement, the patient achieved a complete response with normalization of free light chains, with no detected proteins in the serum. However, despite her lab result improvement, her myopathy continued to worsen clinically. This is when she was referred for auto-SCT.

The patient was given HDM for two days and then infused. Post-transplant, doxycycline 100mg was prescribed as it has been shown to improve outcomes in the settings of cardiac AL amyloidosis [9]. On Day 106 post-transplant, the patient was walking, had no nausea or vomiting, and no other significant clinical symptoms. Some muscle weakness was still there, but otherwise she was recovering well. A MM workup was repeated post-transplant. Her free serum light chain values and K/L ratio continued to remain normal. No abnormal monoclonal protein was detected; the IgG level was normal. The patient continued to improve. At 9 months post-transplant, the patient had a marked decrease in creatinine kinase level compared to the level at initial consultation (189 U/L vs. >1000 U/L). The patient is currently doing very well, with minimal muscle weakness.

Discussion

In the recent literature, reports of skeletal muscle amyloid myopathies have indeed been limited. One of the largest concerns for early diagnosis of amyloidosis is that in a clinical setting, AL amyloidosis may manifest to be other more readily apparent diseases. One of the key factors in this can be attributed to the fact that amyloidosis discovery and diagnosis often requires further

investigation involving biopsies and staining tests, such as the Congo red stain and mass spectrometry. This 63-year old woman was diagnosed with amyloid fibril deposits in her quadriceps and in her vasculature, with minimal involvement elsewhere in the body. After four cycles of CyBorD, the patient showed promising improvement in her labs, but the muscle weakness in her thigh did not improve. Thus, she was treated with high-dose chemotherapy and auto-SCT. She responded positively to the treatment and she regained the strength in her thigh. The purpose of this paper is to highlight high-dose chemotherapy with auto-SCT as an effective treatment strategy for AL amyloid myopathy. However, one potential issue is the heavy toxicity of this treatment strategy; only healthy patients can be offered this option. Despite this, further investigation and the surfacing of similar successful clinical cases could indeed lead to improving outcomes for this patient population.

Conclusion

While this is a single case, auto-SCT has shown remarkable promise in treating vascular amyloidosis. While we are uncertain if HDM and auto-SCT are the only reason for the patient's clinical improvement, it is not unlikely that the patient had a delayed response to the four cycles CyborD and this response was consolidated further with HDM and auto-SCT. This would indicate that amyloidosis is still chemo responsive and there was a cumulative benefit of adding autologous stem cell transplant to the CyBorD treatment. The safety and feasibility of treating vascular amyloidosis with auto-SCT has not been tested or validated to be safe given the concern of vascular involvement and increased mortality from transplant. The patient continued responding positively months post-transplant as her muscle weakness gradually improved.

In cases like this, amyloidosis might minimally involve the bone marrow or hematological parameters but have significant involvement in other organs. Considering chemotherapy with CyBorD followed by upfront auto-SCT has shown to have its benefits, potentially without toxicity. Further trials or studies are needed for investigating the role of novel immune therapies, like daratumumab and other MM-approved drugs, in the setting of systemic amyloidosis of the AL type. In this patient, the clinical response to CyBorD followed by HDM and auto-SCT appears to be a promising strategy. Considering the limited data surrounding auto-SCT in the setting of amyloidosis with major involvement in the skeletal muscle vasculature (without significant involvement of other organs), further investigation is encouraged in order to improve outcomes for this patient population.

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Conflict Of Interest

The authors do not have a conflict of interest.

Author Contributions

Tarek Khedro, Wendy Kadi, Bassam Yaghmour, and George Yaghmour performed the literature search and wrote the manuscript. Wendy Kadi produced the images of the positive Congo red stains.

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