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Chronic myopathy due to immunoglobulin light chain amyloidosis

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Abstract

Amyloid myopathy associated with a plasma cell dyscrasia is a rare cause of muscle hypertrophy. It can be a challenging diagnosis, since pathological findings are often elusive. In addition, the mechanism by which immunoglobulin light-chain deposition stimulates muscle overgrowth remains poorly understood. We present a 53–year old female with a 10-year history of progressive generalized muscle overgrowth. Congo-red staining and immunohistochemistry revealed perivascular lambda light chain amyloid deposits, apparent only in a second muscle biopsy. The numbers of central nuclei and satellite cells were increased, suggesting enhanced muscle progenitor cell formation. Despite the chronicity of the light chain disease, the patient showed complete resolution of hematologic findings and significant improvement of her muscle symptoms following autologous bone marrow transplantation. This case highlights the importance of early diagnosis and therapy for this treatable cause of a chronic myopathy with muscle hypertrophy.

Keywords

Amyloidosis; PAX7; satellite cells; muscle hypertrophy

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1. Introduction

Diffuse muscle hypertrophy is an unusual feature of a chronic myopathy. Abnormally increased muscle bulk may be due to an increase in the number and/or size of muscle fibers, or infiltration of non-contractile materials within the muscle. Generalized muscle hypertrophy or pseudohypertrophy can be the presenting symptom in acquired or hereditary myopathies including amyloidosis, hypothyroidism, acromegaly, muscular dystrophies and non-dystrophic myotonic disorders, lipodystrophy syndromes, and a rare muscle hypertrophy syndrome caused by mutations in myostatin (*MSTN*) [1–5]. We present a case of amyloid myopathy with a 10-year history of isolated muscle pseudohypertrophy before carpal tunnel syndrome, macroglossia, dysphagia and significant fatigue suggested a systemic disease and prompted a repeat muscle biopsy. The patient underwent autologous bone marrow transplantation resulting in remission of immunoglobulin light chain disease and significant improvement in muscle bulk and exercise tolerance. The responsiveness to treatment illustrates the importance of recognizing amyloidosis as a reversible cause of chronic myopathy with muscle hypertrophy, even in the absence of typical symptoms of plasma cell dyscrasias.

2. Case report

A 53-year-old previously healthy female was referred to the NIH Undiagnosed Diseases Program [6, 7] and enrolled in clinical protocol 76-HG-0238, “Diagnosis and Treatment of Patients with Inborn Errors of Metabolism and Other Genetic Disorders” (ClinicalTrials.gov Identifier: NCT00369421). Written, informed consent was obtained. The patient’s chief complaint was generalized muscle overgrowth over the course of ten years; the initial symptoms were increased tightness and pain primarily in the paraspinal muscles. Her muscle bulk increased first in the shoulders and upper arms and subsequently in the thighs, calves, paraspinal and abdominal muscles. There was no history of weight lifting or hormone use. Past medical and family histories were non-contributory.

Although the newly acquired muscle was initially of normal strength, the patient became progressively weaker and eventually limited her daily activities due to fatigue, pain, and claudication of the muscles. By age 51, she developed shortness of breath on exertion and sleep apnea. She required surgical release for carpal tunnel syndrome bilaterally, and developed progressive dysphagia secondary to macroglossia. In the months preceding her NIH admission, she experienced dyspnea with minimal-to-moderate exertion.

Previous neuroimaging evaluations suggested a possible pituitary lesion and she was treated for 6 months with a growth hormone receptor antagonist, pegvisomant, with no effect on the progression of her symptoms. Cardiac evaluations and pulmonary function tests were normal. Electrodiagnostic studies showed changes compatible with a myopathic process, but no increased spontaneous activity or myotonic discharges. Gene testing for lamins A and C to rule out Dunnigan’s partial lipodystrophy was negative for mutations.

A muscle biopsy performed one-year prior to the NIH admission showed muscle fibers of normal shape and size (50–70 microns in diameter), no fiber necrosis or interstitial inflammation, and no evidence of increased glycogen, lipid or mitochondria. Congo red staining did not show amyloid deposition.

On physical examination at the NIH Clinical Center, the patient had diffuse, symmetric enlargement of the skeletal muscles most prominent in the proximal muscles, particularly the shoulder girdle, paraspinal and abdominal muscles (Fig. 1A). The muscles had a solid, hard consistency, but without the definition typically seen among body builders. Muscle strength and endurance were normal in the proximal and distal musculature and there were

no fasciculations, rippling or myotonia. Extraocular movements were intact. The tongue was enlarged with normal strength and no fasciculations. The sensory examination was normal.

MRI of the head showed massive enlargement of he extraocular muscles (Fig. 1B). MRI of the shoulders and thighs showed muscle enlargement but no fatty infiltration, inflammation, or edema (Fig. 1C). An EMG study suggested a non-inflammatory muscle disorder. The arm muscles exhibited early recruitment and short duration, low-amplitude polyphasic motor units compatible with a myopathic process. A right sural nerve conduction study showed decreased amplitude and normal conduction velocity. An echocardiogram showed mild diastolic dysfunction, with an estimated ejection fraction of 65+/−5% and normal right atrial pressure. No freckling was seen. The patient could perform 7 METs (metabolic equivalents) on the Bruce protocol stress test with no desaturation. Cardiac MRI with gadolinium showed increased enhancement of the atrial walls of uncertain significance, but no ventricular involvement (Figure 2A). Pulmonary function testing was within the normal range.

Complete blood count and serum chemistries, including creatine kinase levels, were normal. The pro-brain natriuretic peptide and troponin-I levels were within the normal range. Beta 2 microglobulin was mildly elevated at 2.1 (normal <1.7). Serum and 24-hour urine immunofixation electrophoresis were repeatedly negative for a monoclonal immunoglobulin. Sequencing of the myostatin (*MSTN*) gene, including the 3' UTR, was negative for mutations. *CLCN1* gene testing for non-dystrophic myotonia was also unrevealing.

A left biceps muscle biopsy, analyzed at the Armed Forces Institute of Pathology, revealed amorphous eosinophilic material surrounding several vessels in the endomysium and perimysium (Fig 3A). Congo red staining showed focal apple green birefringence in this material when viewed under polarized light. This material was also strongly positive for amyloid P (Fig. 3B). Immunohistochemistry studies for sarcolemmal and nuclear membrane proteins showed a normal staining pattern, and there was no increased sarcolemmal major histocompatibility complex class I staining. Ultrastructural studies at the National Institutes of Health confirmed the presence of amyloid surrounding the endomysial vessels (Figure 3C and D).

The serum lambda free light chain concentration was 9.34 mg/dl (normal, 0.57–2.63). Kappa free light chain was 1.42 mg/dl (normal range 0.33–1.94), while the ratio of kappa/lambda chain was low at 0.15 (normal 0.26 – 1.65). A bone marrow biopsy confirmed the presence of increased (~10%) lambda-predominant plasma cells (Fig. 3E and F). Congo red staining of the marrow was negative. A skeletal survey did not show lytic or blastic bone lesions.

These findings indicated that amyloid myopathy secondary to systemic AL amyloidosis was the cause of this patient's symptoms. There was no clinical evidence of involvement in other organs such as the liver and kidneys, except for possible involvement of the peripheral nerves.

The patient was referred to the Mayo Clinic Amyloidosis Center and underwent autologous peripheral blood stem cell transplantation four months after her initial presentation at the NIH. She remained stable and experienced significant improvement in the muscle tightness the first month post-transplant. For 3 years following transplantation she continued to note decrease in muscle mass and improvement in exercise tolerance and overall function. Her follow up bone marrow examinations and serum levels of free light chain immunoglobulins remained normal.

In the biceps muscle biopsy obtained at the NIH, further histological evaluation was performed. Compared with a control biceps muscle biopsy from an age- and gender-matched

patient, who did not have a primary neuromuscular disorder, this patient's muscle contained nearly 3 times the number of satellite cells, the skeletal muscle stem cells, as measured by immunofluorescence staining for the satellite cell marker Pax7 (Fig. 4A and B). The number of myofibers with centrally located nuclei was 40 times that of the control (Fig. 4C and D).

3. Discussion

We present a case of an indolent plasma cell dyscrasia producing increased immunoglobulin lambda-chain that resulted in perivascular amyloid deposition over 10 years, triggering skeletal muscle hypertrophy without other systemic manifestations. The muscle hypertrophy was uniform, symmetric and involved almost all muscles including the large paraspinal musculature and small extraocular muscles. Typical features of light chain amyloidosis such as macroglossia, dysphagia, "wooden" consistency of the muscles, and carpal tunnel syndrome were absent during the early phase of the disease. Moreover, serum and urine immunoelectrophoreses for a monoclonal immunoglobulin were repeatedly negative, emphasizing the importance of a high index of clinical suspicion in prompting specific testing for light chain disease and amyloidosis, such as determination of serum free light chains and bone marrow, subcutaneous fat or rectal biopsies.

Diffuse skeletal muscle hypertrophy in the absence of exercise training is a prominent feature in a few neuromuscular disorders, including myotonia congenita and other non-dystrophic myotonic myopathies [8, 9], and in endocrine myopathies secondary to hypothyroidism or acromegaly [10, 11]. Muscle pseudohypertrophy in AL amyloidosis can often be readily differentiated from these other causes on clinical grounds such as the consistency of muscle on palpation, electrophysiologic studies, laboratory testing, and muscle biopsy. Muscle enlargement, described as "pseudohypertrophy" because muscle fiber diameter is not increased, has been reported in 7–44% of amyloidosis cases in different series, depending upon the criteria used to select patients for a muscle biopsy [1]. Patients typically have proximal muscle weakness, fatigue, dysphagia, muscle pseudohypertrophy or palpable tumors/nodules within the muscle that are described to have a "wood-like" consistency [12–16]. Isolated muscle enlargement without other obvious systemic evidence of light chain disease may cause diagnostic confusion.

Unfortunately, delayed diagnosis commonly occurs for this rare form of systemic AL amyloidosis. An asymptomatic period, ranging from 2 weeks to 26 years (mean, 21.7 months), has been reported in a recent review of 79 published cases, and amyloid deposits were not recognized on the initial biopsy in 19 of the patients [17]. The delay in diagnosis can have detrimental consequences since it often results in more extensive, multi-organ involvement that hinders treatment. AL amyloidosis affects the renal, cardiac, hepatic, gastrointestinal, peripheral and autonomic nervous systems, presenting most commonly as nephrotic syndrome, congestive heart failure, peripheral neuropathy, carpal tunnel syndrome or orthostatic hypotension [18–20]. Renal and cardiac failure are the primary causes of death in this disorder, described in 10% and 30%, respectively, of 193 patients in one series [21]. In particular, severe amyloid cardiomyopathy can cause progressive cardiac failure and fatal dysrhythmias [22]. As a consequence, the prognosis of amyloid myopathy is extremely poor, with a mean time to death from the onset of symptoms of about 22 months [17].

On the other hand, early recognition before the onset of cardiac and other systemic manifestations can lead to successful therapeutic interventions. Autologous hematopoietic stem cell transplantation comprises the mainstay of treatment, with an estimated median survival of 40 months in transplant-eligible patients compared to 18 months in patients not eligible for the procedure; eligibility is determined by the degree of systemic disease and is in itself a favorable prognostic factor [23]. Prolonged remissions and reduction of muscle

overgrowth can be achieved with stem cell transplantation [24], although such a gratifying outcome after 10 years of clinical progression is unusual. The rarity of amyloid myopathy precludes large randomized studies for the validation of optimal treatment strategies.

The pathogenesis of generalized muscle hypertrophy in amyloid myopathy remains largely unexplored. Postulated mechanisms include mechanical disruption of muscle contraction by the accumulated amyloid fibrils, impaired muscle metabolism due to abnormal exchange through the thickened vessel wall, ischemia owing to extreme narrowing of the endomysial vessels, and failed electrical conduction due to amyloid deposition beneath the muscle membrane [12, 13, 25, 26]. Hypertrophic fibers larger than 75 micrometers are not commonly detected in amyloid myopathy, leading to the use of the term "pseudohypertrophy" to describe the muscle overgrowth [1]. Although amyloid deposits may account for a portion of the muscle enlargement, amyloid deposition can be minimal or absent in the muscle biopsy.

The generalized and uniform nature of the muscle enlargement suggests a growth-promoting effect of the immunoglobulin light chains or an associated circulating factor that specifically targets muscle. Delaporte et al. elegantly addressed this issue by exposing human muscle cells to the serum of a patient with kappa light chain myeloma-associated amyloid myopathy. The patient's serum had a significant trophic effect on human myoblasts *in vitro* and increased their differentiation, fusion and protein synthesis rather than their proliferation [27]. Since not all patients with a lambda gammopathy develop a myopathy, the effect of the light chain must be specific to the patient, as well as for the muscle.

We investigated whether increased satellite cell proliferation and incorporation into muscle fibers was present in amyloid myopathy. Adult muscle contains a pool of myogenic progenitors or satellite cells, which maintain the capacity to stimulate postnatal muscle growth, repair and regeneration. Satellite cells are mitotically quiescent until they are activated by various stimuli, including stretching, exercise, injury, and electrical stimulation [28, 29]. Upon activation, satellite cells fuse to fibers to cause fiber hypertrophy or fuse together to generate new fibers. Whether satellite cell incorporation into myofibers is required for muscle hypertrophy or whether, in some cases, hypertrophy itself causes satellite cell activation and incorporation is controversial [30, 31]. Our findings raise the possibility that satellite cell activation or proliferation is a feature of amyloid myopathy. Increased internalized nuclei are rare in healthy muscle and indicate regenerated or hypertrophic muscle fibers. The increased prevalence of Pax7-positive cells and fibers with central nuclei as observed in our patient's biopsy suggests enhanced muscle generation. A major limitation of our histological analysis is that we have only a single biopsy from a patient and control. However, the control had satellite cell frequencies similar to what was found in one study of biceps from aged and young men [32], suggesting that our patient has higher than the expected number of satellite cells for a middle aged woman.

Our case underscores that recognition of the clinical features of systemic amyloidosis, and especially the rare presentation of amyloid myopathy, is critical to ensure timely access to aggressive therapy for this otherwise fatal disease. Further studies will be needed to understand the role of light chain in causing muscle hypertrophy and to determine the optimal treatment for this fatal disorder.

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Highlights

- Isolated chronic muscle pseudohypertrophy is a rare presentation of systemic amyloidosis.
- Routine muscle biopsy can be unrevealing and high clinical suspicion is critical for diagnosis.
- Increased satellite cell proliferation may underlie the pathogenesis in this disease.
- Bone marrow transplantation is the only effective treatment if administered timely.

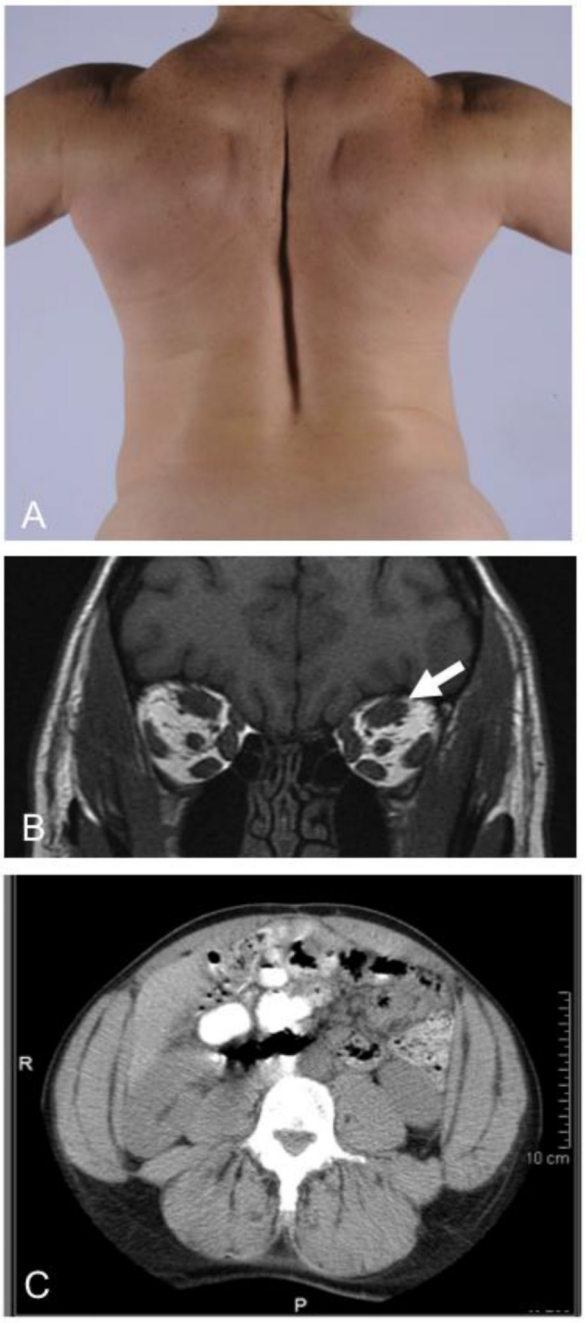

Figure 1. Diffuse and symmetric increase in muscle bulk, more prominent in the shoulder girdle and paraspinal muscles

(A) The patient had the appearance of a weight lifter or body builder. The muscles had a hard consistency and a less defined structure as compared to muscle hypertrophy resulting from exercise. The upper trapezius muscle was particularly prominent, giving the characteristic “shoulder pad” appearance. **(B)** Significant bilateral enlargement of all the extraocular muscles (arrow), the tongue and genioglossus muscle was evident on brain MRI. **(C)** Massive enlargement of the paraspinal muscles was evident on abdominal CT imaging.

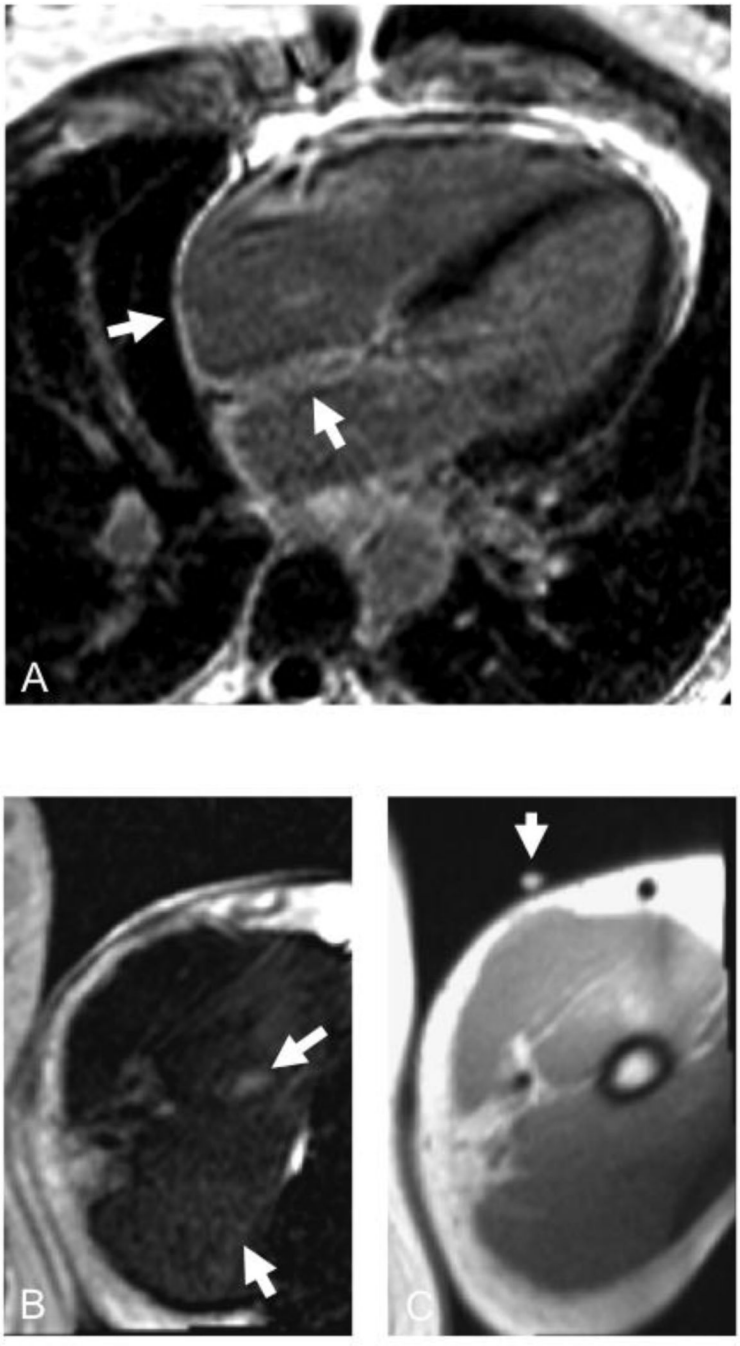

Figure 2. MRI of cardiac and skeletal muscle

(A) Cardiac Cine MRI, a technology allowing visualization of blood flow patterns in the heart and great vessels, shows abnormal late gadolinium enhancement of the atrial walls bilaterally (arrows). In the absence of significant cardiac involvement and without cardiac muscle histology, it is uncertain whether this late enhancement in the atria is due to amyloid deposition. (B) Turbo spin Echo MRI of the deltoid region showed late gadolinium enhancement of the skeletal muscle (arrows). (C) Marker on the skin at the deltoid biopsy scar (arrow,).

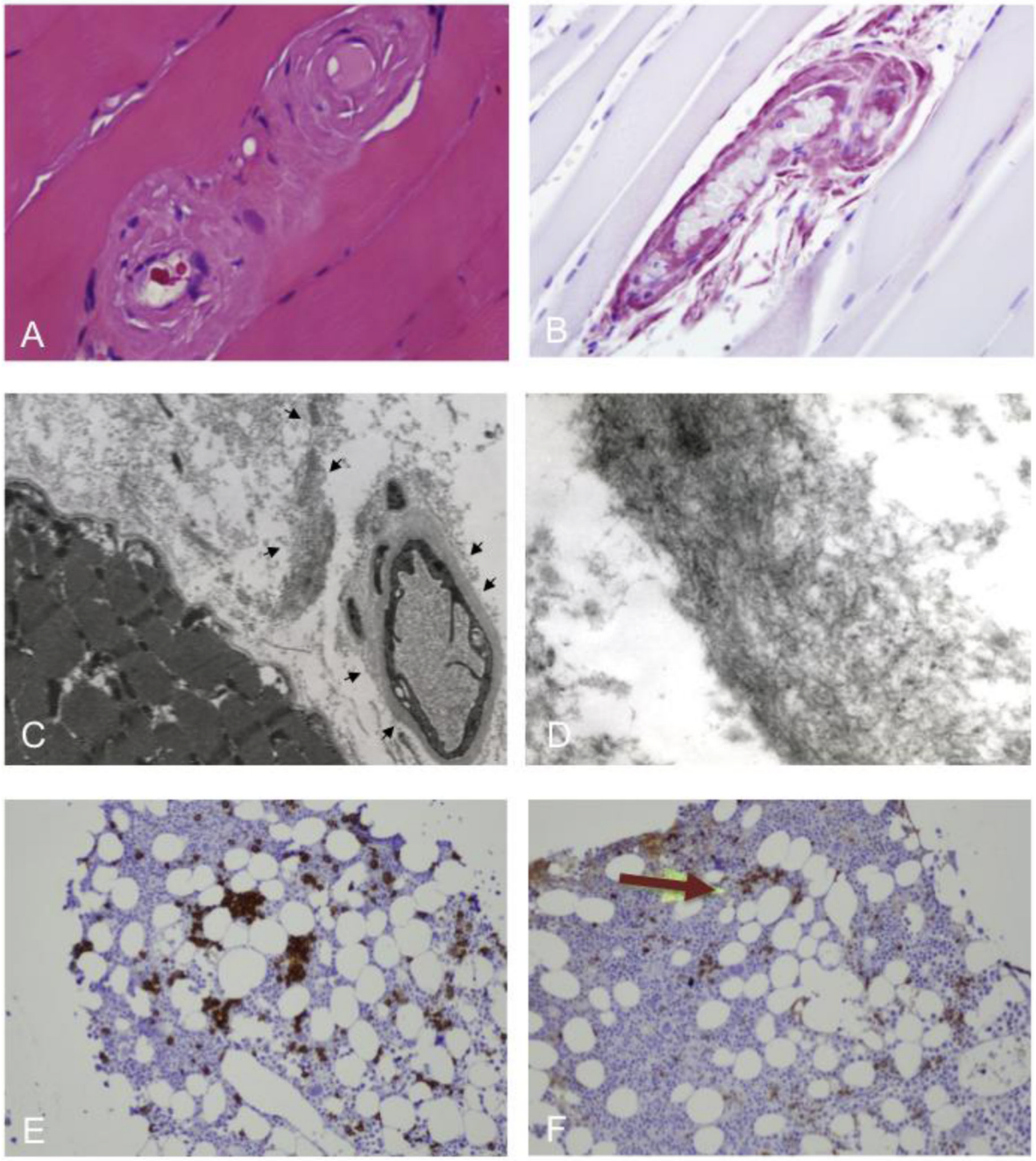

Figure 3. Muscle and bone marrow histology

(A) Increased thickness and hyalinization of the vessel wall and perivascular space within muscle fibers. (**B**) Amyloid P immunostaining of paraffin embedded muscle tissue showed perivascular amyloid deposition. No sarcoplasmic deposits were observed. **(C)** Electron microscopy of the biceps muscle revealed aggregated material in the interstitium, around capillaries (arrows) and on the outer surface of myocytes. (**D**) Higher magnification shows linear, non-branching, randomly oriented fibrils, diagnostic of amyloid. (**E**) Normocellular bone marrow, with small collections of plasma cells, no lymphocytic aggregates, and

negative Congo red staining. CD138 (syndecan-1) immunohistochemistry showed about 10% plasma cells. **(F)** Staining of the marrow for lambda light chain was positive (arrow).

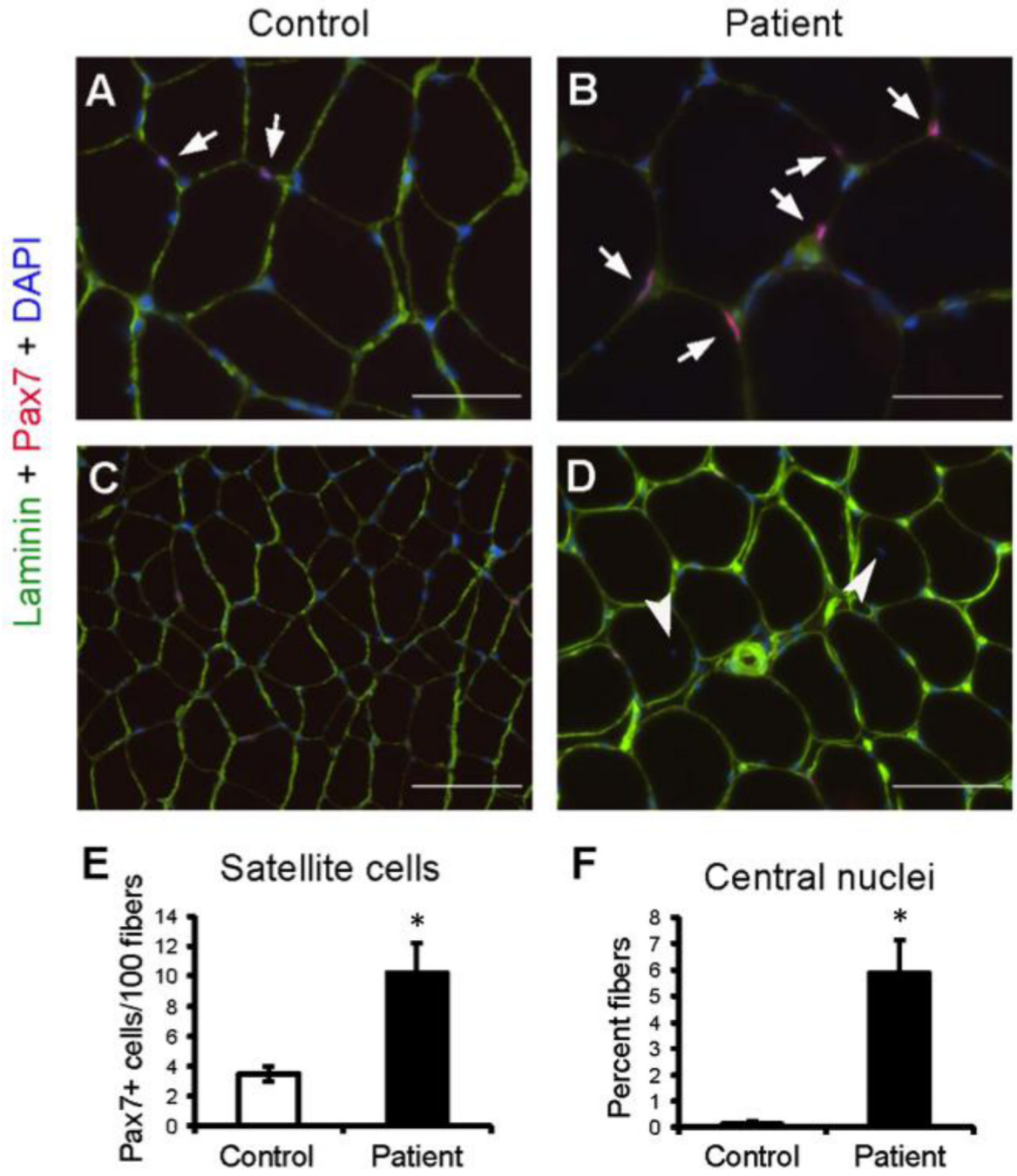

Figure 5. Increased satellite cell number and central nuclei in muscle biopsy

(A–D) Immunofluorescence staining of biceps muscle frozen cross sections in control (**A, C**) and patient (**B, D**) muscle. Patient muscle showed increased numbers of satellite cells and central myonuclei. Satellite cells were stained red (Pax7), nuclei blue (DAPI), and the basement membrane green (laminin) to outline the fibers. Arrows, satellite cells; arrowheads, central nuclei. (**E**) Quantification of the number of satellite cells per 100 myofibers. **(F)** Quantification of the number of myofibers with central nuclei. Ten μm sections were incubated with mouse anti-Pax7 IgG1 hybridoma-conditioned medium diluted 1:10 (Developmental Studies Hybridoma Bank) to stain satellite cells and rabbit anti-laminin

antibody diluted 1:1000 (Sigma) to stain fiber borders. Secondary antibodies were Alexa Fluor 568 conjugated goat anti-mouse IgG1 diluted 1:200 (Invitrogen) and Alexa Fluor 488 conjugated goat anti-rabbit IgG diluted 1:200 (Invitrogen). Sections were mounted in Vectashield mounting reagent containing 4',6-diamidino-2-phenylindole (DAPI) to stain the nuclei (Vector Labs). Every 10^{th} section of serially sectioned biceps muscle was chosen for immunostaining (6 slides from the control and 5 slides from the patient). Counts of fiber number, central nuclei number, and Pax7-positive DAPI-staining cells were made on each slide for a total of 5,571 and 4,153 fibers analyzed from the control and patient, respectively. The data generated for each slide were considered an individual data point and a Students *t*-test was used to compare the control to the patient. Scale bar in A, B = 50 μm; C,D = 100 μm. $*P < 0.001$.