CASE OF THE MONTH

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A 62-year-old woman developed profound weakness secondary to a progressive myopathy associated with primary systemic amyloidosis. The characteristic apple-green birefringent amyloid deposits were demonstrated surrounding individual muscle fibers in Congo red stained sections. Electron microscopy demonstrated amyloid filaments in close apposition to muscle fibers exhibiting excessive corrugations of the sarcolemmal membrane. The pathological features of progressive amyloid myopathy associated with primary systemic amyloidosis are distinct from the intracellular amyloid deposits characteristic of sporadic inclusion body myositis and inherited inclusion body myopathy.
Key words: myopathy • amyloidosis • plasma cell dyscrasia

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AMYLOIDOSIS CAUSING A PROGRESSIVE MYOPATHY

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Inherited and acquired amyloidoses are frequently associated with disorders affecting the peripheral nervous system. Muscle involvement, however, has attracted relatively little attention. In one form of amyloid myopathy findings include: pseudohypertrophy and mild weakness of muscles, macroglossia, and hoarseness of voice.[6,8–10,12–14] In contrast severe, debilitating, progressive muscle weakness[7] as the predominant manifestation of systemic amyloidosis, without concomitant pseudohypertrophy and in the absence of peripheral neuropathy, is exceedingly unusual. The case reported here is an example of the latter.

CASE REPORT

A 62-year-old woman had lower extremity weakness for 1 year. She initially noticed difficulty walking and climbing stairs and subsequently began to fall easily. The weakness progressed so that she was unable to walk without support. She had no trouble chewing or swallowing. There were no sensory complaints. Past medical history was remarkable only for a cholecystectomy. She was maintained on therapeutic doses of warfarin for chronic atrial fibrillation. There was no family history of neuromuscular disease.

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General physical examination showed no abnormalities. Visual acuity, optic fundi, extraocular movements, and facial muscles were normal. Neck flexor strength was not antigravity (MRC grade 2).[4] Muscle weakness was symmetrical in the extremities. In the upper extremities strength was 4- in proximal and 4 in distal muscle groups. In the legs, the hip extensors, flexors, and abductors were grade 2. The knee extensors were 3-, ankle dorsiflexors, evertors, and invertors were 4-. Muscle stretch reflexes were depressed. Plantar responses were flexor. All sensory modalities were preserved.

Laboratory Studies. The results of the following tests were normal: complete blood count, erythrocyte sedimentation rate, BUN, creatinine, electrolytes, blood glucose, vitamin B12, antinuclear antibody, bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and urinalysis. The chest radiograph was normal as were the skeletal survey and radioisotope bone scan. A two-dimensional echocardiogram showed normal heart size.

A creatinine kinase was mildly elevated at 252 U/L (normal <174 U/L). Serum immunofixation demonstrated a monoclonal lambda IgG quantitated at 396 mg/dL. The 24-h urinary protein was 4 gm without demonstrable monoclonal protein or lambda light chains.

Electrodiagnostic evaluation revealed normal sensory and motor nerve conduction studies including sensory nerve action potentials of the median and ulnar nerves (Table 1). Needle EMG of multiple muscles in the arms and legs demonstrated positive waves and fibrillation potentials in

Table 1. Nerve conduction studies of the median and ulnar nerves.

Motor	DL (ms)	CV (m/s)	DA (μv)	PA (μv)	Fwave (ms)
Rt. Ulnar	2.6 (≤3.4)	62 (≥50)	5000 (≥4000)	5000 (≥4000)	26.0 (≤32.0)
Rt. Median	3.0 (≤4.2)	50 (≥50)	4300 (≥4000)	4200 (≥4000)	28.8 (≤31.0)
Sensory					
Rt. Ulnar	1.5	62 (≥50)	11 (≥10)		
Rt. Median	2.4	51 (≥50)	16 (≥10)		

DL = distal latency; CV = conduction velocity; DA = distal amplitude; PA = proximal amplitude.
Normal values in parentheses.

all muscles tested (deltoid, biceps, triceps, vastus lateralis, anterior tibialis). Voluntary motor unit potentials were short in duration and low in amplitude. Recruitment was early and there were many polyphasic units. These findings were consistent with a myopathy.

A left biceps muscle biopsy was performed and processed as previously described.[11] Transverse sections demonstrated scattered regenerating fibers. No inflammatory cells were seen. The most striking finding was the presence of amyloid surrounding individual muscle fibers observed in Congo red stained sections exhibiting characteristic apple-green birefringence under polarizing light (Fig. 1). Intramuscular blood vessels and motor nerve fascicles were free of amyloid deposits. There were no groups of small angular fibers, no type grouping, and no target fibers. Immune staining of the muscle sections using antibody specifically directed against lambda light chains showed deposits surrounding individual muscle fibers corresponding to the distribution of Congo red deposits. Electron microscopy of the biceps muscle demonstrated excessive sarcolemmal folds (corrugations), some attached to the muscle fiber by a mere thread of apposed sarcolemma virtually devoid of intervening sarcoplasm. Amyloid filaments (10–20 nm diameter, nonbranching) were closely intertwined amongst the sarcolemmal corrugations (Fig. 2).

A diagnosis of primary systemic amyloidosis (AL) was conferred following a bone marrow biopsy which showed no evidence of plasmacytosis. The bone marrow biopsy demonstrated amyloid deposits.

The patient was followed for 6 months after diagnosis and continued to worsen. Eighteen months after the onset of symptoms she was confined to a wheelchair.

DISCUSSION

Myopathy associated with extracellular amyloid deposits has been described in only 10 patients.[6–10,12–14] The usual clinical features of amyloid myopathy include: pseudohypertrophy of

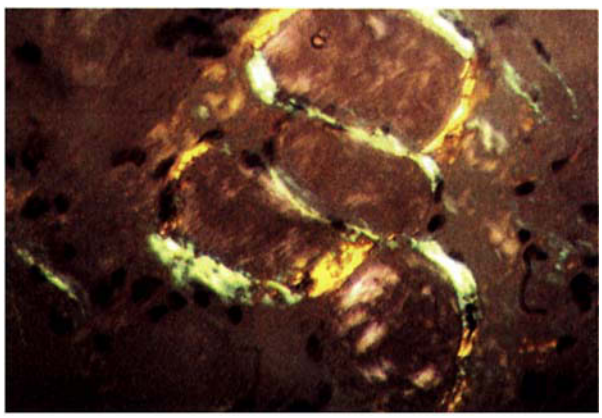

FIGURE 1. Congo red stained transverse cryostat sections of left biceps muscle showing characteristic apple-green birefringent amyloid deposits around individual muscle fibers. (Magnification ×100.)

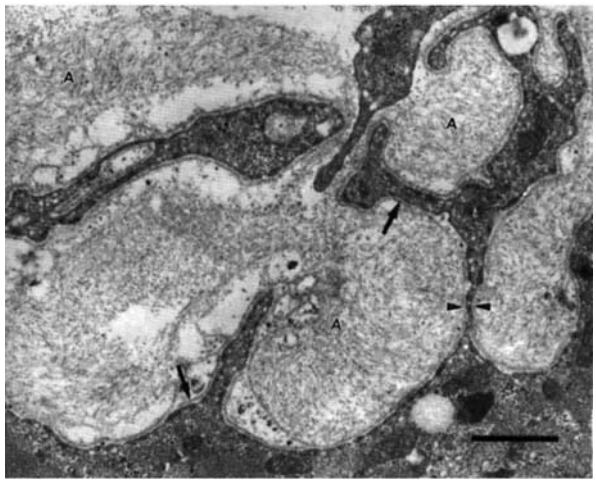

FIGURE 2. Electron micrograph (left biceps muscle) showing excessive sarcolemmal folds (arrows). Some of the sarcolemmal folds are attached to the muscle fiber by a mere thread of apposed sarcolemma devoid of intervening sarcoplasm (arrowheads). Amyloid filaments (10–20 nm diameter) are closely intertwined amongst the sarcolemmal folds (A). Bar length = 1 μm.

muscles, macroglossia, dysphagia, and palpable nodules within the muscle.[6,8–10,12–14] In contrast, progressive muscle weakness as the predominant clinical manifestation of amyloid myopathy, as described in the case under discussion, is rare.[7] Respiratory failure as the presenting manifestation has been described.[1]

All cases of amyloid myopathy have accompanied either primary systemic amyloidosis[1,8,9,12,13] or amyloidosis complicating myeloma.[6,7,14] In either instance, malignant or nonmalignant plasma cell dyscrasia, the amyloid is composed of monoclonal light chains (i.e., AL type). In contrast, myopathy as the predominant clinical manifestation has not been reported in secondary (AA) or familial (AF) amyloidosis. These observations suggest that monoclonal light chain (AL)-associated amyloidosis has a greater affinity for skeletal muscle[15] compared to the aberrant proteins associated with inherited (transthyretin, apolipoprotein A1, gelsolin) or secondary (serum protein AA) forms of amyloidosis. This relationship has potential diagnostic implications.

The mechanism by which extracellular amyloid causes muscle weakness remains unclear. Amyloid deposits have a known predilection for blood vessels and intramuscular nerves but this was not observed in the case under discussion. Neither was there evidence of denervation atrophy (by either muscle biopsy or EMG) nor muscle fiber necrosis. Instead, amyloid filaments were closely adherent and intertwined with the extracellular matrix surrounding individual muscle fibers (Fig. 2). The highly corrugated appearance of the sarcolemmal membrane raises the possibility that the muscle fibers suffer a mechanical limitation. Alternatively, an electromechanical dissociation may exist.

An important pathological distinction to be emphasized in the discussion at hand is the difference between amyloid deposits in inclusion body myositis (IBM)[11] and those observed here. Amyloid in IBM is formed intracellularly and accumulates within muscle fibers. In IBM immune staining shows β-amyloid protein, N- and C-terminal epitopes of amyloid precursor protein, ubiquitin, and tau proteins within the vacuolated muscle fibers.[2,3] The muscle biopsy of the patient under discussion had none of the histological features of IBM; notably absent were rimmed vacuoles, inflammatory infiltrates and intracellular 15–18-nm filaments.[5]

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