Myopathy in primary systemic amyloidosis

Morie A Gertz, Robert A Kyle

Abstract

Objective—To define the natural history of primary systemic amyloidosis when muscle involvement is prominent at presentation.

Methods—A retrospective review was carried out of all patients seen at the tertiary referral practice of the Mayo Clinic between 1 January 1960 and 31 December 1994. All patients with primary systemic amyloidosis and proof of amyloid deposits by muscle biopsy were included for analysis. No patients were lost to follow up.

Results—Twelve patients were identified with amyloidosis in muscle. Muscle involvement was the most prominent symptom in patients who had widespread visceral involvement, which included the heart, peripheral nerve, and tongue. Of the 12, three had skeletal muscle pseudohypertrophy. All patients had a demonstrable dysproteinaemia by the finding of free light chain in the serum or urine, a discrete monoclonal peak on serum or urine protein electrophoresis, or a monoclonal population of plasma cells in the bone marrow. Measurement of creatine kinase was not a useful test. Of eight patients treated with chemotherapy based on alkylating agents, three responded. The median survival for the entire group was 12 months.

Conclusions—The finding of a monoclonal protein in a patient with muscle weakness is an important clue to the diagnosis of primary systemic amyloidosis. Most patients have visceral involvement outside the musculoskeletal system. A subset of patients seems to respond to systemic chemotherapy. The overall survival, however, remains poor, with most patients dying of cardiac failure. Immunoelectrophoresis of serum and urine should be a routine diagnostic test during the evaluation of myopathy of unknown cause.

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Primary systemic amyloidosis is a disorder in which insoluble immunoglobulin light chains form amyloid fibrils. About 90% of patients have a demonstrable monoclonal protein in the serum or urine. The intact heavy chains,

the monoclonal light chain, or its N-terminal fragment are deposited in the tissues as amyloid, resulting in widespread organ dysfunction and death. The most common presentations of patients who have amyloidosis are nephrotic syndrome with or without renal insufficiency, cardiomyopathy, peripheral neuropathy, or hepatomegaly.¹ Muscle involvement represents a well recognised, but rare, manifestation of amyloidosis. This review was undertaken to determine the natural history and to assess whether there would be clinical clues to the diagnosis of systemic amyloidosis.

Materials and methods

A computerised search of the records of all patients seen at the Mayo Clinic with the diagnosis of amyloidosis who had a muscle biopsy was done for the period from 1 January 1960 to the end of December 1994. There were 1596 patients with primary systemic amyloidosis seen in this period. During this period, a total of 224 patients were seen with clinical evidence of amyloid peripheral neuropathy (14%). There were 47 sural nerve biopsies showing amyloid in this group. Each history was reviewed to ensure that the amyloidosis was primary (immunoglobulin light chain) in origin. In addition, the muscle biopsy specimen had to demonstrate deposits of amyloid that stained positively with Congo red and showed green birefringence under polarised light. Permission to perform a retrospective chart review was granted by the institutional review board of the Mayo Foundation in accordance with federal regulations. Patient contact letters were approved by the institutional review board before contact was made.

Results

There were 12 patients identified as having primary systemic amyloidosis with amyloid deposits in muscle (fig 1). The patients were seen between December 1963 and May 1990. All patients were followed up to the end of January 1995 or until they died, and no patients were lost to follow up. The table gives the characteristics of these 12 patients. The men:women ratio was 3:1, and the median age at diagnosis was 63.4 years.

The diagnosis of amyloidosis in muscle was established by biopsy of the vastus lateralis in four patients; hamstring muscle in one; triceps in two; deltoid in two; and biceps, gluteus maximus, and gastrocnemius in one each. Symptoms that led to the muscle biopsy

Department of Hematology and Internal Medicine, Mayo Clinic and Mayo Foundation, Rochester, MN, USA
M A Gertz
R A Kyle

Correspondence to:
Dr M A Gertz, Department of Hematology and Internal Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA.

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Figure 1 Biopsy specimen demonstrates endomysial amyloid deposits (Congo red; $\times 40$) (courtesy of Andrew G Engel).

included specific muscular weakness in all 12 patients, with superimposed more generalised weakness in two; pseudohypertrophy in three; pseudohypertrophy in association with thickening, stiffening, and flexion contractures in one; tender muscles in one; and arm and leg claudication in three. In four of the 12 patients, a diagnosis of amyloidosis had been established at another site 10, 11, 21, and 22 months before a muscle biopsy had been performed.

Most patients had clinical involvement by amyloidosis of other tissues. Half of the patients had associated peripheral neuropathy and half had cardiac involvement. A quarter had nephrotic syndrome. Carpal tunnel syndrome, glossomegaly, purpura, and autonomic neuropathy were seen in four, three, three, and two patients respectively. One third had limb or jaw claudication due to amyloidosis. Three of the four patients had clinically important jaw claudication in addition to limb claudication. Two of the patients had factor X deficiency with measured concentrations of 6% and 56%. One patient had typical amyloid arthropathy.

Serum albumin concentration was depressed in more than half of the patients, ranging from 14 to 38.8 g/l, with a median of 29 g/l. Of the 12 patients, seven had a serum albumin value less than 30 g/l, and all three patients with renal amyloidosis had a serum albumin value less than 26 g/l. These three patients all had nephrotic syndrome, with 8.5, 9.0, and 40 g of proteinuria per day. One of these three also had renal insufficiency, with a serum creatinine concentration of 460 $\mu\text{mol/l}$. Two of the three had hypercholesterolaemia related to their nephrotic syndrome. Creatine kinase concentration was measured for all patients and was increased in two. In both, the creatine kinase concentration

was less than twice the institutional normal value.

As the table shows, all patients had evidence of monoclonal gammopathies. In six patients, a lambda light chain was found in the serum or urine, and in two a kappa light chain was found. One additional patient had cardiac amyloid deposits immunoreactive with kappa immunoglobulin light chain antisera. Three patients did not have a specific light chain identified but had electrophoretic patterns available for review. In one patient (patient 6), a serum M spike of 1.3 g/dl was present on the serum electrophoresis. In one patient (patient 4), urinary protein excretion was 9.1 g, and 81% represented a discrete beta spike in the urine, but immunoelectrophoresis was not performed. A third patient (patient 5) had a serum M component of 1.2 g/dl and also had Bence Jones protein detected in the urine with the Bence Jones heat test. Of the nine patients who had a serum monoclonal protein, the M spike never exceeded 1.3 g/dl. Five of the nine had light chains in the serum only, with no demonstrable peak. In the remaining four patients, the peak ranged from 0.95 to 1.3 g/dl. A urine M spike was detected in eight of the patients. The median urine M protein excretion was 0.32 (range 0.01–7.4) g/day.

In two of the 12 patients, the presence of a monoclonal gammopathy was recognised before the diagnosis of amyloidosis at 10 and 21 months. Symptoms of amyloidosis subsequently developed in the presence of a monoclonal gammopathy of undetermined significance. In addition to all the muscle biopsy specimens, amyloid deposits were found in three of 10 bone marrow biopsy specimens, four of four subcutaneous fat aspirates, seven of seven rectal biopsy specimens, two of three kidney biopsy specimens, two of two

Figure 2 Pronounced tongue enlargement in a patient with amyloid and skeletal muscle pseudohypertrophy (note the facial purpura).

Figure 3 Paraspinal pseudohypertrophy of the skeletal muscles.

heart biopsy specimens, and one lip and one tongue biopsy specimen each.

Electromyographic studies were performed in all 12 patients; evidence of myopathy was seen in 10 and peripheral neuropathy without myopathy in two. Two patients had carpal tunnel syndrome recognised on EMG; three had evidence of both peripheral neuropathy and myopathy. The 12 muscle biopsy specimens showed deposits of amyloid in blood vessels and interstitial spaces in four patients, vascular and epineural deposits in two, vascular deposits only in four, vascular and connective tissue deposits in one, and connective tissue only in one. All three patients with skeletal pseudohypertrophy had large interstitial deposits of amyloid present. In addition, all three patients with skeletal pseudohypertrophy had pronounced enlargement of the tongue (figs 2 and 3).

One patient (patient 3, table) fulfilled the criteria for multiple myeloma in addition to amyloidosis, defined by: (1) renal biopsy demonstration of myeloma cast nephropathy with a discrete urine light chain peak of 0.2 g/day, (2) a bone marrow specimen containing 27% plasma cells, and (3) a bone survey showing rib fractures and osteoporosis. A bone survey was performed in eight other patients and the result was normal in all. One patient (patient 2) had 20% plasma cells in the bone marrow but no other indications of multiple myeloma and was considered as having amyloidosis without myeloma. A bone marrow study was performed in nine other patients and showed an increased number of plasma cells in eight, ranging from 5% to 13% (median 5%).

An ECG was performed in all patients. Abnormalities in T waves were seen in three patients, left axis deviation in two, and a normal pattern in one. One patient each had a right bundle branch block, sinus arrhythmia, and low voltage, often associated with amyloid. Two patients had atrial fibrillation, and

Characteristics of patients amyloid myopathy established by biopsy

Patient	Age (y)	Sex	SIEP	UIEP	Survival (months)	% PCs	Treatment	Result	Cause of death
1	66	F	λ	λ	15.5	—	CTX, MP	No response	Unknown
2	76	M	κ	κ	3.8	20	None	—	Amyloid CHF, lung cancer
3	71	M	κ	κ	17.6	27	MP, CTX	Response	COPD
4	57	F	Not done	Not done but beta spike seen on UPEP	21.4	5	CTX	No response	CHF
5	54	M	Not done but M spike seen on SPEP	Not done but urine Bence Jones grade II	9.2	7	Melphalan	No response	Pneumonia
6	61	M	Not done but M spike seen on SPEP	Not done	2.4	5	None	—	Amyloid
7	55	M	Gλ	λ	1.7	13	None	—	CHF
8	53	F	0	λ	148+	5	MP	Response	Alive
9	66	M	Gλ	0	68.4	5	MP	Response	MDS, CHF, progressive myopathy
10	74	M	λ	λ	7.2	5	MP	No response	CHF
11	55	M	λ	λ	35.5	5	Colchicine	No response	Amyloidosis, colitis
12	70	M	Cardiac amyloid deposits κ+	0	4.8	7.5	MP	No response	CHF, hypotension, ventricular tachycardia, heart block

CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CTX = cyclophosphamide; MDS = myelodysplastic syndrome; MP = melphalan and prednisone; SIEP = serum immunoelectrophoresis; SPEP = serum protein electrophoresis; UIEP = urine immunoelectrophoresis; UPEP = urine protein electrophoresis.

three showed a pseudoinfarction pattern typical of amyloidosis. As well as the six patients who had cardiac amyloid at diagnosis, congestive heart failure developed in one additional patient subsequent to the diagnosis of amyloid peripheral neuropathy and myopathy.

An echocardiogram was performed in eight patients and showed changes diagnostic of amyloid in six—two with concentric left ventricular hypertrophy and four others with classic infiltration and stiffening of the myocardial wall—and was not diagnostic in two. The interventricular septum measured from 10 to 15 mm in all patients, with a median of 12.5 mm. Only one patient had depression of the ejection fraction to 50%; ejection fraction was normal in the other seven.

Chemotherapy was given to eight patients, colchicine to one, and no treatment to three. The untreated patients died after 2.3, 1.8, and 3.9 months. Of the patients who received treatment, clinical evidence of a response was shown in three. In one patient (patient 9), treated with melphalan and prednisone, the M protein disappeared from the serum, and a previously increased creatine kinase value returned to normal. This patient, who presented with cardiac failure, ultimately survived 68 months. The second patient (patient 8) treated with melphalan and prednisone presented with severe neck weakness and proximal myopathy with factor X deficiency and also had resolution of congestive heart failure, eradication of lambda light chain from the urine, and normalisation of both the severely depressed factor X concentration and creatine kinase concentration. This patient remains alive after 13 years. The third patient (patient 3), who was treated with melphalan, prednisone, and cyclophosphamide, had eradication of kappa light chains from serum and urine, stabilisation of peripheral neuropathy, and improvement in muscle weakness. This patient ultimately died at 18 months of chronic obstructive pulmonary disease unrelated to the amyloidosis. Treatment was not innocuous; pancytopenia and a myelodysplastic syndrome developed in one of the three responders and contributed to his death. Chromosome analysis showed changes consistent with a myelodysplastic syndrome attributable to melphalan treatment (44,XY,-5,-7,-12,-17,t[5;17]t[7;12]). The median survival for the entire group was 12 months. Only two patients survived more than five years.

Discussion

The first recognised patient with amyloid involvement of muscle was reported by Lubarsch² in 1929 and showed both vascular and interstitial deposits in skeletal muscle and the heart. Nonetheless, amyloidosis is a rare cause of myopathy, even in those patients with a recognised dysproteinaemia. In 10 patients with monoclonal gammopathy and myopathy, amyloidosis was not found in any muscle biopsy specimens.³

Amyloidosis is a well recognised cause of adult onset sensory-motor peripheral neuropathy,

and one of seven patients with amyloidosis has peripheral neuropathy. In a review of 10 patients with amyloid peripheral neuropathy, only three had muscle weakness even though muscle biopsy specimens showed atrophic muscle fibres in all. Histological evidence of myopathy must, therefore, be distinguished from clinical evidence.⁴ In the current report, all patients had muscular weakness as a prominent component of their evaluation and presenting symptoms. This led to the performance of a muscle biopsy for clinical purposes as part of the investigation of weakness. Muscle pseudohypertrophy associated with amyloid has long been known⁵⁻⁸ and was present in three of the 12 patients we have reported. The three patients we saw with skeletal pseudohypertrophy also had massive enlargement of the tongue (figs 2 and 3), and this association is supported by previous reports.

Muscle weakness caused by amyloid myopathy has been described in the absence of pseudohypertrophy, and this was the situation in nine of our 12 patients. The clinical picture in this situation is proximal muscle weakness with pronounced atrophy, often with inability to raise the arms above the head or to climb stairs.⁹ Weakness of the neck flexors and shoulder and thigh muscles with atrophy is common. One of our patients (patient 9) had difficulty climbing stairs and was unable to squat or bend owing to the severity of the muscle weakness. A second patient in this group (patient 8) had such severe neck weakness that she had to hold her head with her hands when changing from the supine to the upright position or her head would hyperextend. She also had difficulty climbing stairs, walking, or rising from a stool. This group of patients did not have macroglossia, and weakness with atrophy was the only manifestation of amyloidosis in four. The lack of distinguishing clinical characteristics in the atrophic form of amyloid myopathy merits emphasis. The history and physical findings are nondescript compared with other forms of myopathy, and in these patients, the only clinical clue was the presence of the monoclonal protein, which has become a routine screening tool in the evaluation of myopathy at our institution.

Clinically, pseudohypertrophy is easy to recognise, and the differential diagnosis is narrow. In fact, many patients with amyloid muscle pseudohypertrophy were omitted from this study because these patients presented to the clinician with obvious amyloid pseudohypertrophy and were diagnosed by using less invasive techniques such as subcutaneous fat aspiration or rectal biopsy and never underwent skeletal muscle biopsy, which was a requirement for inclusion in this study. On the other hand, the atrophic form of amyloidosis is much harder to recognise as such, and these patients went directly to muscle biopsy for confirmation of a diagnosis because amyloidosis was often omitted from the differential diagnosis. In the four patients with pre-existing amyloidosis, a muscle biopsy was performed because the clinical findings were so

nondescript that the responsible clinician could not be certain that the myopathic symptoms were due to the amyloid.

Of the three types of systemic amyloidosis, it is the primary systemic amyloidosis type that most often has involvement of skeletal muscle. Amyloid is generally not deposited in the muscle in the secondary type (AA) and can occasionally be seen in transthyretin (familial) forms of amyloidosis.¹⁰ Others have reported amyloid myopathy and familial amyloidosis.¹¹ One of our patients had amyloidosis associated with myeloma, and the presence of amyloid myopathy with myeloma and lytic bone disease has previously been recognised.¹²

Although not seen in our group, amyloid myopathy involving the diaphragm and resulting in diaphragmatic failure requiring ventilatory support is well recognised.¹³⁻¹⁵ In this setting, survival is generally short, and respiratory failure is the cause of death.

Claudication was seen in four of our patients and has been recognised in patients with amyloid myopathy.^{16,17} It results from progressive vascular deposition of amyloid and leads to ischaemia and obstruction of small vessels. These patients have in the past been misdiagnosed as having giant cell arteritis and inappropriately treated with high dose corticosteroids.

Skeletal amyloidosis has been evaluated by CT,¹⁸ MRI,¹⁹ technetium-99m methylene diphosphonate,²⁰ and technetium 99m-pyrophosphate.²¹ None of these procedures are diagnostic, and biopsy is still required to confirm the diagnosis. Magnetic resonance imaging that shows pronounced articulation of the subcutaneous fat is distinctive. Soft tissue uptake of amyloid has been recognised for many years, but the differential diagnosis remains broad. It has been hypothesised that the high calcium content of amyloid deposits that binds the serum amyloid P component also binds the radionuclide. Scintigraphic studies with radioiodinated serum amyloid P component have been used to evaluate amyloid deposits in vivo. Moreover, quantitative turnover studies can measure the total body burden of amyloid and can show whether amyloid deposits are being mobilised after chemotherapy.²²

The mechanism whereby the amyloid deposits produce dysfunction of skeletal muscle remains relatively unknown. Hypotheses that have been proposed include amyloid mechanically interfering with muscle function, amyloid accumulating in vessels and causing ischaemic atrophy in muscle fibres, and amyloid accumulating on the sarcolemmal membrane and interfering with electrical conduction along the muscle fibre.²³ Amyloid deposition has been recognised histopathologically as causing compression atrophy of muscle fibres¹⁰ and ischaemic atrophy owing to extreme narrowing of capillaries when skeletal pseudohypertrophy is not present.²⁴ Muscle contraction could be restricted by impaired tissue elasticity due to the amyloid deposition. The infiltration around muscle cells could lead to muscle distortion, and the vascular infiltra-

tion might also interfere with clearance of metabolic waste products from the muscles. The role of action potential propagation down the sarcolemmal membrane remains unknown.²⁵

This report constitutes the largest number of patients with amyloid identified histopathologically at premortem muscle biopsy. The study design introduces bias because of its retrospective nature. Patients with clearcut muscle involvement who did not undergo muscle biopsy would have been excluded from analysis. There are patients whose disease is diagnosed by less invasive techniques, such as rectal biopsy or subcutaneous fat aspirate, and these patients would have been omitted. We think that skeletal pseudohypertrophy is underrepresented because the dramatic clinical presentation suggests the diagnosis and would lead to biopsy of more accessible tissues. Patients considered too sick for biopsy would also be excluded. This analysis, limited to those patients with muscle biopsy diagnosis, may not be representative of all patients with clinical evidence of muscle involvement. Patients in this study were selected for biopsy at the discretion of their physicians and based on the clinical features of their weakness.

An important clue to the recognition of this disease, particularly when pseudohypertrophy is not present, is the demonstration of a monoclonal gammopathy in serum or urine. Immunoelectrophoresis or immunofixation should be considered mandatory in the evaluation of a patient with a myopathy. Also, none of the patients in this group presented with myopathy alone. Often there was an associated peripheral neuropathy, and in one patient, there was arthropathy. Seven of the 12 patients had subsequent evidence of cardiac or renal amyloid deposits. Only one of 12 patients had neither peripheral neuropathy nor cardiac amyloidosis. This patient had amyloid arthropathy and macroglossia. The survival with this disease remains poor. A median survival of just over one year was found in this study. There was a subset of patients that had objective benefit from chemotherapy. Amyloid myopathy responsive to chemotherapy with melphalan and prednisone has been reported by others as well.²⁶ Given the poor prognosis associated with this disorder, it seems that a trial of chemotherapy would be reasonable in all patients.

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