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Systemic Immunoglobulin Light Chain Amyloidosis–Associated Myopathy: Presentation, Diagnostic Pitfalls, and Outcome

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Abstract

Objective: To characterize the natural history of immunoglobulin light chain amyloidosis–associated myopathy and to provide guidelines for recognition.

Patients and Methods: Fifty-one patients with systemic immunoglobulin light chain amyloidosis and biopsy-confirmed muscle amyloid deposition diagnosed between January 1, 1995, and December 31, 2015, were included in this study.

Results: Common presenting symptoms were muscle weakness in 49 patients (96%), dysphagia in 23 (45%), myalgia in 17 (33%), macroglossia in 17 (33%), jaw claudication in 13 (25%), and hoarseness in 9 (18%). The median time from the onset of symptoms to diagnosis was almost 2 years. Less than two-thirds of the patients with an outside muscle biopsy (16 of 27) had an established pathologic confirmation of amyloidosis due to failure to routinely incorporate Congo red staining. Moreover, 12 patients were incorrectly treated before diagnosis of amyloid myopathy. More than half of the patients had normal creatine kinase levels at diagnosis. Cardiac troponin T levels were elevated above the reference range in 5 of 12 patients who lacked evidence of cardiac involvement. Median overall survival was 32 months. Factors associated with inferior survival were involvement of more than 2 organs (median survival, 13 months), cardiac involvement (median survival, 15 months), and absence of stem cell transplant (median survival, 18 months). With the exclusion of patients treated with stem cell transplant, no improvement in survival was seen over the 1995-2004 and 2005-2015 decades.

Conclusion: Immunoglobulin light chain amyloidosis–associated myopathy is rare. Delay in diagnosis is common, and there is a high rate of pathologic and clinical misdiagnosis. Awareness of elevation of cardiac troponin T levels in the absence of cardiac disease may be a clue to diagnosis.

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Clinical Vignette

A 68-year-old man had development of progressive muscle weakness over a 12-month period. The muscle weakness was associated with a declining ability to climb stairs, walk, rise from a sitting position, comb his hair, or reach for overhead objects. He had no limitations with writing, buttoning, or dressing, no muscle pain, and no sensory symptoms. An unintentional weight loss of 10 kg was reported. Physical examination revealed proximal muscle atrophy and weakness, with a Trendelenburg gait pattern. A complete blood cell count yielded a hemoglobin level of 12 g/dL but no other abnormalities. Other laboratory results included the following (reference ranges provided parenthetically): sedimentation rate, 22 mm/1h (0-22 mm/1h); C-reactive protein,

15.9 mg/L (≤8.0 mg/L); creatine kinase, 1528 U/L (52-336 U/L); and aldolase, 15.7 U/L (<7.7 U/L). Polymyalgia rheumatica (PMR) was diagnosed, and the patient was given prednisone, 60 mg/d. Prednisone was discontinued when PMR was excluded because of a lack of myalgia or stiffness and the prominent muscle weakness, uncharacteristic of PMR. Electromyography revealed a proximal myopathy with fibrillation potentials. A muscle biopsy was obtained while prednisone was reinitiated with the addition of methotrexate weekly for presumed inflammatory myopathy. The biopsy revealed numerous necrotic and regenerating fibers indicating an active myopathy, but the absence of a mononuclear cell infiltrate excluded the diagnosis of inflammatory myopathy. A Congo red–stained section revealed congophilic deposits in the perimysium and endomysium, occasionally encasing muscle fibers, and in many blood vessel walls. Further evaluation documented bone marrow clonal plasma cells and a small monoclonal IgA κ band on serum electrophoresis and immunofixation coupled with an elevated (21.3 mg/dL) serum κ free light chain (0.33-1.94 mg/dL) with an abnormal free light chain ratio of 23.4 (0.26-1.65). Systemic immunoglobulin light chain amyloidosis–associated myopathy was diagnosed, and melphalan and dexamethasone treatment was initiated.

Immunoglobulin light chain (AL) amyloidosis is a clonal plasma cell disorder characterized by the deposition of fibrillary monoclonal immunoglobulin light chains in tissues leading to organ dysfunction. The most commonly involved organs are the heart, kidneys, liver, gastrointestinal tract (GIT), and peripheral and/or autonomic nerves.[1] Deposition can occur in any organ and tissue. Because AL amyloidosis is a disorder with an estimated incidence of 3 to 10 per million persons per year,[2,3] muscle involvement is not well characterized, which may lead to a delay in diagnosis.[4]

Immunoglobulin light chain amyloidosis presenting with muscle involvement is rare. The published literature on this amyloid syndrome consists mainly of case reports, with one case series of 12 patients.[5] This study was undertaken to review our experience with AL amyloid myopathy, describe the clinical features that correlate with amyloid myopathy, and describe pitfalls in the diagnosis.

PATIENTS AND METHODS

Among 3434 patients with AL amyloidosis seen at our clinic between January 1, 1995, and December 31, 2015, 51 (1.5%) had a muscle biopsy positive for amyloid deposition. All patients gave written informed consent for use of their medical records. The study was approved by the institutional review board in accordance with federal regulations.

The diagnosis of amyloidosis was based on a muscle biopsy revealing congophilic extracellular deposition viewed under rhodamine optics. All patients underwent evaluation that included blood and urine tests for monoclonal immunoglobulin as well as screening for other involved organs. Amyloid typing as AL (by immunohistochemistry, immunofluorescence, or mass spectrometry) was available for 35 patients (69%). Organ involvement was defined by consensus criteria.[6] For cardiac biomarker evaluation among patients with cardiac involvement, we compared 24 patients of the study cohort who had cardiac involvement and available cardiac biomarker measurements with a cohort of 726 cardiac amyloidosis patients who did not have amyloid myopathy.

Descriptive statistics were given as median and range, and the Kruskal-Wallis test was used to ascertain differences between continuous variables. The Kaplan-Meier method was used for survival analysis, with the log-rank test used to compare groups. $P<.05$ was considered significant. Statistical analysis was performed using JMP software (SAS Institute).

RESULTS

The median age of the patients was 67 years (range, 43-82 years), and 36 of the 51 patients (71%) were male. All but one patient had newly diagnosed AL amyloidosis. In one patient, myopathic symptoms developed early in the disease course.

Clinical Manifestations

Clinical features of amyloid myopathy are presented in the Table and in Figure 1. Forty-nine (96%) patients had proximal muscle weakness, and one-half had distal muscle weakness. Other reported muscular symptoms included myalgia in 17 patients (33%), atrophy in 13 (25%), pseudohypertrophy in 6 (12%), muscle claudication in 6 (12%), tenderness in 4 (8%),