

## Diaphragm paralysis in primary systemic amyloidosis

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**Keywords:** *Amyloidosis, diaphragm paralysis, neuropathy, non-invasive ventilation*

**Abbreviations:** *ADM, abductor digiti minimi; APB, abductor pollicis brevis; EMG, electromyography; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; MAG, myelin-associated glycoprotein; MGUS, monoclonal gammopathy of unknown significance; NCS, nerve conduction studies; PA, pulmonary artery; Pdi<sub>max</sub>, maximal transdiaphragmatic pressure; Pi<sub>max</sub>, maximal inspiratory pressure; Pe<sub>max</sub>, maximal expiratory pressure; Pg, gastric pressure; Ppl, pleural pressure; RA, right atrial; RV, right ventricle*

### Abstract

A patient with primary (AL) systemic amyloidosis developed mononeuropathy multiplex complicated by diaphragmatic failure. High dose melphalan and autologous stem cell transplantation did not ameliorate neuropathy or diaphragm dysfunction. Nocturnal non-invasive ventilation lowered arterial carbon dioxide levels and improved daytime dyspnea. This is the first case associating AL amyloid-induced neuropathy with diaphragm dysfunction.

### Introduction

Organ dysfunction in primary systemic (AL) amyloidosis results from tissue deposition of insoluble fibrils composed of monoclonal immunoglobulin protein. The heart, kidneys, liver and nervous system are most frequently involved. Three case reports attribute diaphragm dysfunction in systemic amyloidosis to an infiltrative myopathy without associated neuropathy [1–3]. We report a case of diaphragm paralysis complicating AL amyloid-induced mononeuropathy multiplex.

### Case report

A 65 year-old woman presented with worsening dyspnea and new orthopnea. Immunoelectrophoresis 4 years earlier detected IgG  $\kappa$  monoclonal gammopathy of unknown significance (MGUS) accompanied by right radial neuropathy and left vocal cord paralysis. Electromyography (EMG) and nerve conduction studies (NCS) diagnosed multiple sensory and motor mononeuropathies involving the right and left median, right ulnar and right radial nerves (Tables I and II). Peroneal motor and sensory responses were normal. Neither conduction block nor small, polyphasic ('myopathic') muscle

units were detected. Sural nerve biopsies were non-diagnostic. Weakness was confined to muscles innervated by the affected nerves on NCS. Creatine phosphokinase levels were normal. Antibodies to acetylcholine receptor, ganglioside, myelin sulfatide, myelin-associated glycoprotein (MAG) and Hu epitopes were negative. Rheumatoid factor, anti-nuclear antibodies, cryoglobulins, antineutrophilic cytoplasmic antibodies, HIV and hepatitis B and C virus titers were unremarkable. Serum glucose levels were normal on multiple occasions. Chest X-ray demonstrated right hemidiaphragm elevation (Figure 1). MRI studies identified normal cervical and thoracic spine foramen, and diffuse adenopathy. Cervical lymph node biopsy documented amyloid deposits. She was referred to the Amyloid Treatment and Research Program at Boston University where IgG  $\kappa$  AL amyloidosis was diagnosed by monoclonal protein expression on serum immunofixation electrophoresis, congophilia on fat pad aspirate, and bone marrow clonal plasma cell expansion with  $\kappa$  light chain over-expression. Organ involvement was limited to the peripheral nervous system and lymph nodes. The patient underwent treatment with high dose intravenous melphalan (200 mg/M<sup>2</sup>) and autologous stem cell transplantation. Persistent plasma

Table I. Motor nerve conduction studies.

Stimulation site	Record site	Latency (ms) (normal)	Amplitude (mV) (normal)	Velocity (m/s) (normal)
Right median wrist elbow	APB*	3.1 (< 4.4)	1.2 (> 4.2) 1.1	46 (> 49)
Left median wrist elbow	APB*	4.1 (< 4.4)	2.0 (> 4.2) 1.1	37 (> 49)
Right ulnar wrist below elbow above elbow	ADM**	3.3 (< 3.5)	9.6 (> 5.6) 9.7 8.5	61 (> 49) 51

\*APB, abductor pollicis brevis; \*\*ADM, abductor digiti minimi.

Table II. Sensory nerve conduction studies.

Stimulation site	Record site	Latency (ms) (normal)	Amplitude (uV) (normal)	Velocity (m/s) (normal)
R. median sensory digit II	wrist	3.5 (< 3.5)	99.4 (> 10)	38 (> 41)
L. median sensory digit II	wrist	no response		
R. ulnar sensory digit V	wrist	3.0 (< 2.9)	12.0 (> 5)	36 (> 39)
R. radial sensory wrist	snuff box	2.2 (< 2.7)	6.6 (> 18)	46 (> 44)

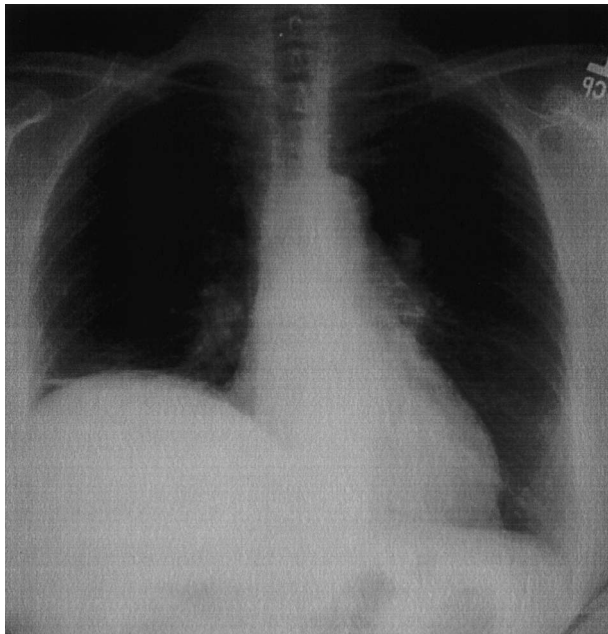


Figure 1. Right hemidiaphragm elevation. PA chest radiograph demonstrating marked upward displacement of the right hemidiaphragm.

cell dyscrasia post-transplant prompted 3 months salvage therapy with intermittent dexamethasone.

Four months later, dyspnea and orthopnea worsened. Mediastinal adenopathy and right diaphragm

elevation remained unchanged by CT imaging. Right heart catheterization recorded RA pressure of 7, RV 40/13, PA 35/12 (mean 22), and wedge pressure of 10 mmHg. Fluoroscopic 'sniff testing' revealed minimal left and absent right hemidiaphragm movement. Upright spirometry (FEV<sub>1</sub> 0.77 L (49% predicted) and FVC 0.94 L (42%)) decreased 46% when repeated supine. Room air arterial blood gas documented hypercarbia (PaCO<sub>2</sub> 49 torr) and normal alveolar-arterial oxygen difference. Static respiratory muscle functions were significantly decreased: maximal inspiratory pressure (P<sub>i,max</sub>) of 30.9 (normal > 75 cmH<sub>2</sub>O) and maximal expiratory pressure (P<sub>e,max</sub>) of 76 cmH<sub>2</sub>O (normal > 150). Esophageal and gastric balloon manometry recorded trans-diaphragmatic pressures (P<sub>di,max</sub>) of 5.64 cmH<sub>2</sub>O, consistent with diaphragm paralysis (Figure 2). Noninvasive nocturnal ventilation resolved the orthopnea, lowered PaCO<sub>2</sub> (45 torr) levels, and improved daytime exercise tolerance.

## Discussion

We document bilateral diaphragmatic paralysis in a patient with AL amyloidosis. Patients with neuromuscular disease require a P<sub>di,max</sub> of 40 cmH<sub>2</sub>O to sustain unsupported ventilation [4]; our patient had a P<sub>di,max</sub> of 5 cmH<sub>2</sub>O. Weak accessory respiratory

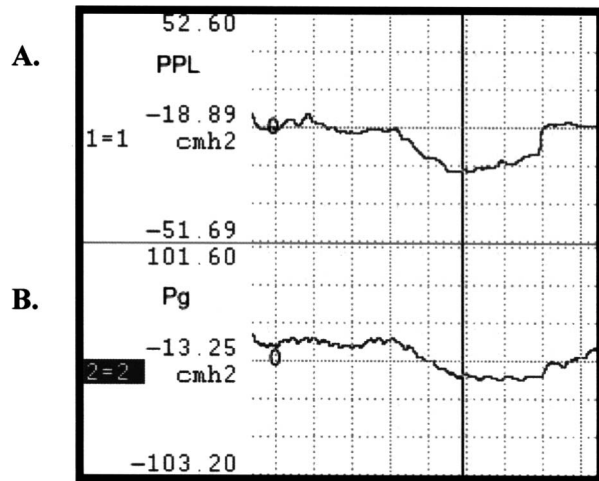


Figure 2. Diaphragm paralysis by manometric measures. A. Pleural pressures (Ppl) obtained during maximal inspiratory maneuver by a balloon positioned in the mid-esophagus. B. Gastric pressures (Pg) during the same inspiratory maneuver.  $P_{di_{max}}$  measured 5.64 cmH<sub>2</sub>O.

muscles compounded the problem. Hypercarbia and dependence on nocturnal mechanical ventilation provided clinical confirmation of respiratory muscle failure.

Three case reports describe diaphragm weakness in patients with systemic amyloidosis – two with multiple myeloma and one with undefined amyloid [1–3]. Our patient represents the first report of diaphragm paralysis in primary systemic (AL) amyloidosis. Prior cases documented diaphragmatic amyloid deposits surrounding vessels or atrophic smooth muscle fibers, without clinical or histologic signs of neuropathy. Diaphragm dysfunction in these cases was attributed to amyloid-related disruption of muscle fiber length–tension properties or to the compressive effects of extracellular ‘amyloid muscle pseudohypertrophy’ [3].

Our data offer a different apparent mechanism of disease: AL amyloid-induced phrenic nerve damage. Multiple motor and sensory neuropathies preceded diaphragm dysfunction, fulfilling criteria for mononeuropathy multiplex. The neuropathies progressed despite bone marrow ablation and stem cell transplantation for AL amyloidosis, ultimately disrupting diaphragm function. Normal proximal muscle strength and absence of myopathic signs on repeated EMG studies excluded primary amyloid myopathy. Additionally, unilateral hemidiaphragm elevation is characteristic of phrenic nerve disorders, not infiltrative diaphragmatic myopathies.

Mononeuropathy multiplex is an unusual neurologic presentation of AL amyloidosis [5]. Polyneuropathy complicates AL amyloidosis in 17–35% of cases, typified by symmetric distal sensorimotor axonal degeneration affecting small nerve fiber function [6,7]. Over the past 7 years, we

treated 99 AL patients with severe peripheral neuropathy manifest as symmetric lower extremity paresthesias and sensory loss. None developed mononeuropathy multiplex or diaphragm paralysis. A related condition, MGUS-associated multifocal motor neuropathy, can induce phrenic paralysis [8], however co-existent sensory deficits, lack of conduction block, and absence of ganglioside antibodies excluded that diagnosis. Myasthenia gravis was ruled out by normal extraocular and bulbar muscle function with undetectable anti-acetylcholine receptor antibody titers.

The mechanism by which AL amyloidosis induces axonal nerve degeneration is unknown. Biopsies documenting endoneurial vascular infiltration or perivascular amyloid deposition support ischemic injury to the nerve, while compressive injury might occur from extraneural deposits [6,9]. Alternatively, circulating free light chain may injure small nerve fibers by increasing cellular oxidative stress [10,11].

Treatment toxicities could cause diaphragm paralysis. Our patient received melphalan and glucocorticoids. Melphalan has never been associated with diaphragm paralysis or respiratory muscle dysfunction. In contrast, chronic dexamethasone administration induces types I and II fiber atrophy in rat diaphragms [12], implicating it in respiratory muscle weakness. Despite treating 37 AL patients with a dexamethasone salvage protocol at Boston University, steroid-related respiratory muscle failure has not occurred.

Amyloid-adenopathy accompanied our patient’s disease. Lymph node injury to recurrent laryngeal and phrenic nerves occurs in cancers and granulomatous diseases [13]. Similarly, neurofibromata induce diaphragm paralysis by compressing cervical nerves exiting the spine [14]. CT and MRI studies of our patient excluded foraminal pathology of the cervical spine or enlarged lymph nodes positioned along the course of the right phrenic nerve.

We report the first case of diaphragm paralysis in a patient with AL amyloidosis. Amyloid-induced mononeuropathy multiplex offers a new potential mechanism of phrenic nerve injury. Patients with AL disease and mononeuropathy multiplex should have respiratory muscle function checked periodically.

### Acknowledgments

The authors gratefully acknowledge expert support and contributions of staff from the Stem Cell and Amyloid Treatment and Research Programs. Supported by grants from NIH (HL 68705), FDA (FD-R-002532-01), the Gerry Foundation, the Young Family Amyloid Research Fund, and the Amyloid Research Fund at Boston University.

**References**

1. Ashe J, Borel CO, Hart G, Humphrey RL, Derrick DA, Kunkel RW. Amyloid myopathy presenting with respiratory failure. *J Neurol Neurosurg Psychiatry* 1992;55:162-165.
2. Streeten EA, de la Monte SM, Kennedy TP. Amyloid infiltration of the diaphragm as a cause of respiratory failure. *Chest* 1986;89:760-762.
3. Santiago RM, Scharnhorst D, Ratkin G, Crouch EC. Respiratory muscle weakness and ventilatory failure in AL amyloidosis with muscular pseudohypertrophy. *Am J Med* 1987;83:175-178.
4. Mier-Jedrzejowicz A, Brophy C, Moxham J, Green M. Assessment of diaphragm weakness. *Am Rev Respir Dis* 1988;137:877-883.
5. Vucic S, Chong PST, Cros D. Atypical presentations of primary amyloid neuropathy. *Muscle Nerve* 2003;28: 696-702.
6. Duston MA, Skinner M, Anderson J, Cohen AS. Peripheral neuropathy as an early marker of AL amyloidosis. *Arch Intern Med* 1989;149:358-360.
7. Kyle RA, Gertz MA. Primary systemic amyloidosis: clinical and laboratory features in 464 cases. *Semin. Hematol* 1995; 32(1):45-59.
8. Beydoun SR, Copeland D. Bilateral phrenic neuropathy as a presenting feature of multifocal motor neuropathy with conduction block. *Muscle Nerve* 2000;23:556-559.
9. Kelly JJ Jr, Kyle RA, O'Brien PC, Dyck PJ. The natural history of peripheral neuropathy in primary systemic amyloidosis. *Ann Neurol* 1979;6:1-7.
10. Trotter JL, Engle WK, Ignaczak TF. Amyloidosis with plasma cell dyscrasia: an overlooked cause of adult onset sensorimotor neuropathy. *Arch Neurol* 1977;34:209-214.
11. Brenner DA, Jain M, Pimentel DR, Wang B, Connors LH, Skinner M, Apstein CS, Liao R. Human amyloidogenic light chains directly impair cardiomyocyte function through an increase in cellular oxidant stress. *Circ Res* 2004;94(8): 1008-1010.
12. Prezant DJ, Karwa ML, Richner B, Maggiore D, Gentry EI, Chung V, Cahill J. Short-term vs long-term dexamethasone treatment: effects on rat diaphragm structure and function. *Lung* 1998;176:267-280.
13. Robinson LR, Brownsberger R, Raghu G. Respiratory failure and hypoventilation secondary to neurosarcoidosis. *Am J Respir Crit Care Med* 1998;157(4 Pt 1):1316-1318.
14. Hassoun PM, Celli BR. Bilateral diaphragm paralysis secondary to central von Recklinghausen's disease. *Chest* 2000; 117:1196-1200.