Intermittent Claudication as the Presenting Symptom in Primary Amyloidosis

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Intermittent claudication is a symptom of circulatory insufficiency that develops primarily in muscles of the lower extremities. It is most frequently associated with atherosclerosis, but may also occur with other vascular disorders such as giant cell arteritis, thromboangiitis obliterans, Takayasu disease and Raynaud disease, as well as with stenosis of the lumbar spinal canal [1]. Here we report on a patient whose symptoms of intermittent claudication appear to be due to amyloid angiopathy; moreover, this appears to be the first symptom of this patient's previously unrecognized primary amyloidosis.

A 77-year-old man presents with a 4-year history of exercise-induced pain in his calf muscles bilaterally, extending to his thighs and buttocks. These symptoms now occur after walking approximately 50 yards and are relieved completely by resting for a few minutes. He also has pain in both upper extremities with minimal exercise, relieved by rest. Approximately 18 months ago he underwent a laminectomy of L4 and decompression of L3-4 and L4-5 for spinal stenosis, but his symptoms remained unchanged. Neurologic reevaluations indicate that his persisting symptoms of intermittent claudication are not due to spinal stenosis. Multiple peripheral vascular studies, including an angiogram and ankle brachial index with exercise, have all indicated no major vascular obstruction.

On physical exam he is normotensive, with no bruits and nontender temporal arteries. The liver is moderately enlarged, and the spleen is not palpable. Straight leg raise is negative. Motor and sensory examinations are intact throughout. There is some degree of cyanosis of his feet, particularly in the dependent position, and the distal extremities are cool, but distal pulses and capillary refill are normal.

Laboratory tests reveal a blood urea nitrogen of 28 mg/dl and a creatinine of 1.7 mg/dl. Blood count reveals a mild anemia with a hemoglobin of 11.9 g/dl and hematocrit of 36%. The white blood cell count is 4,300/ml with 22% lymphocytes, 17% monocytes, 5% eosinophils and 1% basophils. The platelet count is 37,000/ml.

Serum protein electrophoresis shows increased β -globulins (1.19 g/dl, normal 0.6–1.10) with normal levels of albumin, α_1 , α_2 - and γ -globulins. Quantitative levels of IgG, IgA, IgM, κ and λ

chains, the ratio of heavy-to-light chains and the ratio of κ - to λ light chains are all within normal limits. Urine protein electrophoresis on concentrated urine revealed a large β_2 globulin peak (51% the total urine protein concentration of 530 mg/dl). Analysis of the β_2 component by immunoelectrophoresis indicated that the major component is transferrin, but some κ light chains were also present. No heavy chains were associated with these κ chains, nor were there any λ light chains. The presence of more transferrin than albumin in the urine with only a small amount of monoclonal κ light chains is highly unusual. In the nephrotic syndrome, for example, the major urine protein is albumin, with a small amount of transferrin. In renal damage secondary to a monoclonal gammopathy, the monoclonal immunoglobulin component is usually the major urine protein, followed by albumin and transferrin. The small amount of κ light chains in the urine of this patient contrasts with the impressive deposits found within the blood vessel walls in his skin and muscle biopsies.

Biopsies were obtained from the patient's rectus femoris muscle and overlying skin. Congo red staining demonstrated amorphous deposits within vessel walls in both skin and muscle and displayed an intense yellow-green bi-

Fig. 1. Photomicrographs of blood vessels in quadriceps muscle. Left: routine illumination showing waxy-appearing material in vessel walls. Right: the same field viewed under polarized light demonstrating yellow-green birefringence characteristic of amyloid in the vessel walls. Congo red. $\times 68$.

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refringence with polarized light (fig. 1), establishing the diagnosis of amyloid angiopathy. With permanganate treatment the yellow-green birefringence did not persist, indicating that this is not AA amyloid. Immunohistochemical studies show positive peroxidase reactions in the blood vessel walls with primary antibodies directed against AL amyloid, and specifically with antibody to κ light chains, while λ light chains were negative. The amorphous material within the vessel walls did not stain with a monoclonal antibody to AA amyloid seen in secondary amyloidosis. Otherwise, the muscle and skin showed no pathologic abnormalities. These histologic and immunohistochemical studies clearly confirm the diagnosis of amyloid angiopathy, and indicate that this is a primary amyloidosis with deposition of κ light chains. One may expect such results to be associated with a myelodyscrasia such as multiple myeloma, but the etiology in this patient is not clear. His bone marrow biopsy showed a small increase in percentage of plasma cells (5%), but this does not meet the criteria for diagnosis of multiple myeloma.

Intermittent claudication in association with amyloidosis has been reported only rarely [2-6]. Amyloid infiltrates numerous organ systems including blood vessel walls, particularly the media of small arteries and arterioles. Zelis et al. [4] have measured forearm blood flow response in affected subjects and have shown that amyloid infiltration may cause a decreased dilator capacity of resistance vessels. Thus these vessels are restricted in their ability to accommodate the requisite increase in blood flow with exercise, which leads to muscle ischemia and the symptoms of claudication.

Amyloid angiopathy is most often associated with intracerebral hemorrhage in the elderly [7], but pathologic studies of cerebral amyloid angiopathy frequently refer to ischemic changes [8, 9]

and have demonstrated multiple microinfarcts in the cerebral cortex, leading to the suggestion that transient ischemic attacks (TIA) may be a clinical manifestation of this phenomenon [10]. Interestingly our patient had suffered a TIA approximately 13 years ago and a subendocardial myocardial infarction 3 years ago, both of which may be due to his microvascular amyloid angiopathy.

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