Systemic primary amyloidosis in chronic hemodialysis

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A patient with end-stage renal disease undergoing chronic hemodialysis presented with disseminated systemic primary amyloidosis without evidence of ?2-microglobulin deposition. Multiorgan involvement proved by biopsy was present in breast, lymph nodes, gastric mucosa, and bone marrow. Imaging studies and biochemical testing revealed evidence suggesting involvement of other organ systems, including thyroid, heart, liver, and adrenal gland. It is emphasized that amyloidosis may present with myriad clinical features. Appropriate subclassification of amyloid protein is imperative for defining intervention and treatment.

AMYLOID

Amyloid is a generic term relating to tissue deposition of various fibrillar proteins in a variety of diseases. We describe a patient who had been on chronic hemodialysis for 5 years and presented with disseminated systemic primary amyloidosis without evidence of ?2-microglobulin deposition. Biopsy-proved multiorgan involvement was demonstrated in lymph nodes, breast, bone marrow, and gastric mucosa. The patient also was hypothyroid, with a positive technetium bone scan suggesting amyloid deposition. In addition, probable cardiac, liver, and adrenal involvement was present.

CASE REPORT

A 57-year-old African American woman presented to Baylor University Medical Center (BUMC) in July 1995 with the chief complaint of left arm swelling. Past medical history was remarkable for end-stage renal disease (ESRD), presumed to be secondary to hypertension. The patient had been on chronic hemodialysis, 3 times a week for 5 years.

Admission physical examination revealed a supine blood pressure of 80/40 mm Hg (the patient was asymptomatic) and a pulse of 80 beats per minute. The patient had bilateral axillary lymphadenopathy (left > right), thyromegaly, hepatosplenomegaly, and bilateral breast swelling. Purpura and macroGLOSSIA were absent.

Admission laboratory testing was remarkable for a blood urea nitrogen of 71 mg/dL and a serum creatinine of 4.3 mg/dL, consistent with ESRD. Total bilirubin was 3.5 mg/dL; alkaline phosphatase, 839 U/L; g-glutamyltransferase, 834 U/L; aspartate transferase, 162 U/L; and alanine aminotransferase, 78 U/L. The patient had a hematocrit of 26% and a hemoglobin of 8.1 g/dL, consistent with her chronic renal failure. Further laboratory evaluation revealed negative antimitochondrial and anti–smooth muscle antibodies. Hepatitis B and C serologies were negative. Thyroid-stimulating hormone was elevated at 12.4 ?IU/L, with a total T4 level of 3.4 ?g/dL. Serum cortisol was low, and the corticotropin stimulation test was consistent with adrenal insufficiency.
(corticotropin level, 40 pg/mL; follicle-stimulating hormone level, 22.2 IU/L). Electrocardiogram revealed normal sinus rhythm with voltage criteria positive for left ventricular hypertrophy.

Computed tomography (CT) scan of the chest showed bilateral axillary lymphadenopathy (left > right), an enlarged thyroid gland, and moderate cardiomegaly. Abdominal CT scan was remarkable for hepatosplenomegaly and multiple pancreatic cysts. Both kidneys were small with numerous cysts, consistent with ESRD. A bone scan was suggestive of extensive amyloid deposition in the thyroid gland (Figures 1 and 2). The patient had a right axillary lymph node biopsy that revealed follicular hyperplasia and amyloid deposition. Bone marrow biopsy revealed approximately 7% polyclonal plasmacytosis, erythroid hypoplasia consistent with ESRD, renal osteodystrophy, and vascular amyloidosis. Immunohistochemical stains for κ and λ light chains showed a plasma cell population of 7% to 9%, positive staining of the plasma cells, and a κ-to- λ ratio of 4.5:1. Left breast biopsy revealed diffuse hemorrhage, early degeneration with early fat necrosis, no evidence of carcinoma, and extensive deposition of amyloid material.

Special stains performed both at BUMC and the Mayo Clinic on paraffin-embedded tissue sections from a left breast biopsy revealed that the amyloid deposit stained with antibodies to the P component. Staining with antibodies directed toward light-chain components was positive to κ light chains but negative to λ light chains, thus giving an equivocal result. Antibodies to β2-microglobulin, amyloid-associated serum protein, and albumin were negative. These findings were consistent with the diagnosis of primary amyloidosis. No liver biopsy was done because of the fear of potential severe bleeding complications. Serum immunoelectrophoresis confirmed a monoclonal immunoglobulin G spike of 1632 mg/dL. An echocardiogram revealed a mildly depressed left ventricular ejection fraction of 50%; moderate to severe left ventricular hypertrophy with thickening of all myocardial walls, including atrial and ventricular septa; thickening of all valves; and a sparkling, granular appearance of the myocardium (Figure 3). These findings were consistent with amyloid infiltration of the heart.

The patient was treated with levothyroxine sodium (Syn-throid) for hypothyroidism and hydrocortisone for adrenal insufficiency, and she was discharged on colchicine, 0.6 mg per day, for amyloidosis.

One week later, the patient was readmitted with a massive upper gastrointestinal hemorrhage and a hematocrit of 13%. After blood transfusions and hemodynamic stabilization, she underwent upper gastrointestinal endoscopy that revealed multiple nodules in the stomach. Biopsies of the gastric nodules revealed diffuse amyloidosis in the perivascular distribution. Again, immunohistochemical stains were negative for β2-microglobulin.

The patient did remarkably well on chronic hemodialysis for the next 3 months, but then presented to BUMC with dyspnea and weight loss. Repeat cardiac evaluation showed a very low voltage electrocardiogram and a first degree A-V block. A repeat echocardiogram revealed the same valvular and myocardial change consistent with amyloid infiltration; however, the ejection fraction was now significantly reduced to approximately 15%.

During the next 6 weeks, the patient developed tachyarrhythmias and progressively worse congestive heart failure. She died at the end of December 1995. Permission for an autopsy was not obtained.
DISCUSSION

Historically, amyloidosis was classified according to whether it occurred de novo (primary) or was secondary to a recognizable preexisting or coexisting chronic infectious or inflammatory disease (1). Systemic amyloidosis can be classified according to the biochemical nature of the fibrillar deposit (2). Primary amyloidosis (AL, immunocyte-derived) is a plasma cell dyscrasia resulting in deposition of monoclonal immunoglobulin light chain (Bence Jones protein) or light-chain fragments. Reactive amyloidosis is secondary to chronic inflammation and is associated with the deposition of a fragment of an acute phase reactant, serum amyloid A. Hereditary amyloidosis represents an autosomal-dominant disease caused by mutant forms of the transthyretin protein or other proteins. Finally, dialysis-related amyloidosis (A?2M) is defined by the ?2-microglobulin nature of the amyloid fibrils and occurs in patients who have been on long-term dialysis treatment, usually >8 years.

All amyloid proteins have common morphologic and physical properties. They have a ?-pleated sheet conformation that is responsible for the apple-green birefringence under polarized light after Congo red staining and a typical fibrillar appearance on electron microscopy. In addition, several distinct types of amyloid protein have been identified in the past 3 decades, many of which circulate in the blood before being deposited in extracellular sites. Despite these similarities in morphologic and physical properties, the clinical manifestations of systemic amyloidosis vary widely and depend on the organ systems predominantly involved. The case presented here has several unusual features that merit this discussion.

First, our patient developed ESRD 5 years earlier, ostensibly secondary to hypertensive nephrosclerosis. Hypertension remains the second most common cause for ESRD after diabetes mellitus, yet this patient might have had primary amyloidosis involving her kidneys that led to renal failure. Against this possibility is the long duration of hemodialysis 5 years before other organ system involvement appeared, and the small size of her kidneys on CT scan that is more consistent with hypertensive nephrosclerosis.

When the patient did present with systemic amyloidosis, the organs involved were unusual (breast, lymph nodes, and thyroid). Primary amyloidosis may rarely present as lymphadenopathy (3-6) or as breast masses (7). Amyloid deposition in the thyroid may result in a goiter (8,9), but presenting with frank hypothyroidism is indeed rare. This patient had a significantly elevated thyroid-stimulating hormone, a low T4 level, and a technetium pyrophosphate bone scan consistent with massive amyloid deposition in the thyroid gland (see Figures 1 and 2). All of these findings point to clinically significant hypothyroidism secondary to amyloidosis.

Subsequently, the patient developed upper gastrointestinal hemorrhage due to amyloid deposition in the gastric mucosa. Gastrointestinal tract manifestations with primary amyloidosis are not unusual and may include macroglossia, dysphasia, motility disturbances, diarrhea, malabsorption syndrome, bleeding, infarction, and perforation (2). More recently, A?2M involving the colon and leading to lower gastrointestinal bleeding and infarction also has been described (10) (Fenves AZ, Lerman MJ, Emmett M: Acute intestinal infarction associated with intestinal ?2-microglobulin deposition in chronic hemodialysis patients. J Am Soc Nephrol 1994;4:445 [abstract]) (Price DA, Gunes B, Turner JR, Lazarus JM, Kay J: Beta2-microglobulin [A?2M] amyloidosis involving the GI tract in hemodialysis [HD]. J Am Soc Nephrol 1995;6:558 [abstract]).
An additional unusual feature was the presence of Addison’s disease, manifested by hypotension, a low serum cortisol level, an adrenocorticotropic hormone stimulation test consistent with the diagnosis of adrenal insufficiency, and a prompt clinical response to hydrocortisone. The hypotension also may have been an early manifestation of an autonomic insufficiency, which can accompany primary systemic amyloidosis. Because there was no tissue diagnosis, the etiology of the adrenal insufficiency is in question, although amyloid involvement seems quite possible in this patient. Panhypopituitarism from destruction of the pituitary by amyloid deposits has been reported (11).

The patient also had hepatosplenomegaly, as demonstrated by physical examination and by CT scan, a common finding in disseminated systemic amyloidosis. The elevated liver function tests were consistent with this diagnosis as well. There appeared to be little or no cardiac dysfunction initially, with preserved left ventricular function and no evidence of cardiac conduction defects. Subsequently, the electrocardiogram revealed extremely low voltage in the limb leads, and a repeat 2-dimensional echocardiogram was consistent with significant cardiac amyloid deposition and severely compromised left ventricular systolic function. The patient eventually developed a first-degree A-V block and tachyarrhythmias, probably related to this condition. The ultimate cause of death was refractory cardiac failure.

When the patient was first diagnosed with amyloidosis, we considered the possibility of Aβ2M, despite the relatively short duration of hemodialysis. However, x-rays of both wrists failed to show carpal bone cysts, and the tissue distribution of amyloid in this patient was highly atypical for Aβ2M. Immunohistochemical stains of several of the biopsy tissues were repeatedly negative for β2-microglobulin at both BUMC and the Mayo Clinic, further excluding this diagnosis. Staining for immunoglobulin light chains was suggestive of a pathologic predominance, and this, along with the clinical picture (i.e., the results of serum electrophoresis and marrow findings), was consistent with primary amyloidosis. A monoclonal immunoglobulin component in serum or urine is detectable by immunoelectrophoresis in about 80% of patients with primary amyloidosis; however, in contrast to multiple myeloma, Bence Jones proteins are more frequent than Bence Jones proteins in Aβ2M (2). This patient also was unusual in this regard, because she had a pathologic monoclonal light chain.

Amyloidosis, similar to many other diseases, can present with myriad clinical features. Common associations (e.g., chronic inflammation and secondary amyloidosis, or chronic hemodialysis and elevated levels of β2-microglobulin) are helpful in formulating a differential diagnosis, but they are unreliable in establishing a definitive answer. Furthermore, demonstrating the presence of amyloid protein by apple-green birefringence under polarized light microscopy after Congo red staining is not a sufficient endpoint. Diligence is imperative when amyloid protein is identified in a biopsy specimen, because subclassification is critically dependent on further biochemical testing. Appropriate differentiation of amyloid type then affords specific intervention and treatment.

**Acknowledgment**
The authors wish to thank Ann Drew for her assistance in preparing this manuscript.
References


