Clinicopathological Conference

Congestive Heart Failure in a 70-Year-Old Man

James T. Willerson, MD; Phoebe C. Chen, MD; Elizabeth A. Hartwell, MD; L. Maximilian Buja, MD

Case History

A 70-year-old man was admitted to Hermann Hospital, Houston, Tex, for further evaluation of progressive dyspnea on exertion and pedal edema. He had an evaluation for congestive heart failure 18 months earlier in another city, including coronary angiography, which revealed normal coronary arteries, an echocardiogram, which showed mild left ventricular systolic dysfunction without hypertrophy or dilatation, and a myocardial biopsy reported to show focal amyloid deposition.

He initially had improved symptomatically with the therapeutic regimen of an angiotension converting enzyme inhibitor and diuretics, but he had noticed progressive dyspnea on exertion during the previous 6 months. He was able to walk one-half mile before experiencing dyspnea 6 months ago, but lately he only could perform household chores before experiencing dyspnea. He experienced transient substernal chest discomfort with exertion every 1 to 2 weeks that lasted seconds to a few minutes and was relieved by rest. He stated that the pains did not radiate and were “mild.” In addition, he denied nausea, diaphoresis, light headedness, or palpitations with the chest discomfort. He did have two-pillow orthopnea. There was no paroxysmal nocturnal dyspnea, fever, chills, syncope, light headedness, gastrointestinal or genitourinary blood loss, dysuria, urinary retention, weight loss, diarrhea, constipation, dysphagia, or hoarseness.

Past medical history was significant for a diagnosis of pernicious anemia made 10 years before admission, left hemispheric cerebrovascular accident with no residual deficits 2 years before admission, and hepatitis soon after World War II. Medications on admission included 20 mg furosemide PO BID, 5 mg enalapril maleate PO BID, 300 mg ranitidine hydrochloride PO every day, 1 mg folate PO every day, two 325-mg enteric-coated aspirin PO BID, and monthly vitamin B12 injections. Family history was significant for coronary artery disease in his parents, who both lived into their 70s. He was a retired journalist. He did not travel outside of the United States, and he drank one or two 1-oz glasses of whiskey every night. He had a 10 pack-year history of cigarette smoking, having quit 30 years ago.

Physical Examination

Physical examination revealed a well-nourished man in no acute distress. He was alert and oriented to time, place, and situation. Height was 68 in., and weight was 150 lb. Vital signs revealed a temperature of 98.4°F; pulse, 68 and regular; respirations, 16, supine blood pressure, 110/60 mm Hg; and upright blood pressure, 110/65 mm Hg. Head examination was normocephalic with clear sclaeae; pupils were equally round and reactive to light and accommodation; extraocular movements were intact; optic discs were sharp; tympanic membranes were clear; no sinus tenderness or discharge was present; and the oropharynx was clear. The tongue was not abnormally large. The neck was supple without thyromegaly, lymphadenopathy, or jugular venous distention. Carotid upstrokes were of normal intensity bilaterally without bruits. Lungs were clear to auscultation bilaterally.

Cardiovascular examination revealed a normal point of maximal impulse, normal S1 and S2, and a short ejection click with a I/VI systolic ejection murmur in the aortic area. No S3, S4, or rubs were noted. The abdomen was nontender with normoactive bowel sounds. No hepatosplennomegaly, bruits, fluid wave, or dullness to percussion was noted. Genitourinary examination was within normal limits. Rectal examination revealed normal sphincter tone; a nontender, mildly enlarged prostate; and a negative guaiac test. Extremities were without clubbing, cyanosis, or edema. Neurological examination was within normal limits. Musculoskeletal examination revealed normal strength and tone in all major muscle groups, full range of motion in all major joints, and no overt joint swelling or deformities. Skin examination revealed scattered actinic keratoses and a few cherry angiomas without other overt lesions, telangiectasias, or scratch purpura.

Hospital Course

The patient was admitted, and an extensive workup was initiated. This resulted in comprehensive data, including chemical analyses (Table 1), ECG (Fig 1), and radiographs (Figs 2 to 4). Serum protein electrophoresis revealed a monoclonal spike in the gamma region, and subsequent immunofixation electrophoresis revealed immunoglobulin G-κ monoclonal bands in the serum and free κ light chains in the urine. Cardiac workup consisted of a resting multiple gated acquisition radionuclide ventriculogram scan, which showed an ejection fraction of 0.48; a 24-hour Holter monitor ECG, which had a predominant normal sinus rhythm with rare multiform premature ventricular contractions; and an echocardiogram,
Table 1. Laboratory Data—Blood and Urine

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value (reference)</th>
<th>Value (reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mEq/L)</td>
<td>135 (135 to 145)</td>
<td>AST (U/L)</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>4.0 (3.5 to 5.0)</td>
<td>24 (7 to 40)</td>
</tr>
<tr>
<td>Chloride (mEq/L)</td>
<td>105 (95 to 105)</td>
<td>Alkaline phosphatase (U/L)</td>
</tr>
<tr>
<td>CO₂ (mEq/L)</td>
<td>24 (24 to 32)</td>
<td>80 (34 to 108)</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>89 (65 to 110)</td>
<td>Lactic dehydrogenase (U/L)</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.7 (0.5 to 1.4)</td>
<td>212 (83 to 200)</td>
</tr>
<tr>
<td>Urea nitrogen (mg/dL)</td>
<td>25 (10 to 20)</td>
<td>Creatine kinase (U/L)</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>7.6 (2.5 to 8.0)</td>
<td>169 (12 to 191)</td>
</tr>
<tr>
<td>Total protein (g/dL)</td>
<td>25 (6.0 to 8.0)</td>
<td>Cholesterol (mg/dL)</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.4 (2.8 to 4.3)</td>
<td>150 (150 to 200)</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>9.0 (8.5 to 11.0)</td>
<td>Triglycerides (mg/dL)</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>2.7 (2.5 to 4.5)</td>
<td>105 (45 to 170)</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>44 (7 to 40)</td>
<td>Total bilirubin (mg/dL)</td>
</tr>
<tr>
<td>Amylase (U/L)</td>
<td>78 (12 to 204)</td>
<td>0.4 (0.2 to 1.0)</td>
</tr>
<tr>
<td>PSA (ng/mL)</td>
<td>1.4 (0.3 to 2.7)</td>
<td>WBC (×10⁹)</td>
</tr>
<tr>
<td>CEA (ng/mL)</td>
<td>4 (0 to 4)</td>
<td>Hemoglobin (g/dL)</td>
</tr>
</tbody>
</table>

Urine (random) Specific gravity, 1.010
pH 6.0,
trace protein,
all else negative

Urine (24 h) Creatinine clearance, 66 mL/min
protein, 180 mg

ALT indicates alanine transaminase (SGPT); PSA, prostate specific antigen; CEA, carcinoembryonic antigen; AST, aspartate transaminase (SGOT); WBC, white blood cell count; MCV, mean corpuscular volume; PT, prothrombin time; PTT, partial thromboplastin time; and TIBC, total iron-binding capacity.

which revealed a left ventricle that was normal in size and function, mild mitral regurgitation, aortic regurgitation, tricuspid regurgitation, mild left atrial dilatation, and a small pericardial effusion. A bone marrow aspirate revealed 20% plasma cells with atypical forms and absent iron stores. Diagnostic procedures were performed.

Radiographic Findings (Phoebe Chen, MD)

Our patient had radiographs of the lumbar spine that showed mild demineralization and degenerative changes (Fig 2). A skull radiograph was unremarkable (Fig 3), and radiographs of the cervical spine showed degenerative changes in C6 and C7. No lytic lesions of the skeleton were identified. A CAT scan of the brain showed some cortical atrophy proportional to the patient's age. No abnormal masses, midline shift, or hydrocephalus was identified. A series of chest radiographs were obtained over a 3-week period. The first chest radiograph (Fig 4) showed mild hyperexpansion of the lungs suggestive of chronic obstructive pulmonary disease. No focal consol-

Fig 1. ECG showing normal sinus rhythm with first-degree atrioventricular block and an interventricular conduction defect; PR interval, 222 milliseconds; QRS, 100 milliseconds; and poor recordal R-wave progression and Q-waves in the septal and lateral leads. There is borderline low voltage.
idation was seen, and the heart was normal in size. The next chest radiograph, obtained after a myocardial biopsy procedure, showed that a large right-sided pneumothorax had developed. A right-sided chest tube was placed as shown in the next chest radiograph with partial reexpansion of the right lung. Pleural thickening of the right lung base was noted. The last chest radiograph showed continued resolution of the right basilar pleural thickening and full reexpansion of the right lung. The right chest tube has been removed.

Case Discussion (James T. Willerson, MD)

This man was referred for further evaluation and determination of whether the limited amyloid deposits demonstrated in his heart by biopsy 18 months earlier might be more extensive now and potentially the cause of his heart failure and for an evaluation of whether he had systemic amyloidosis. An earlier cardiac catheterization and myocardial biopsy had shown limited deposits of amyloid as evidenced by its typical appearance with Congo red stain. His coronary arteriograms were normal. Initially, the clinical considerations were whether the patient should have a heart transplant, whether the amyloid was limited to his heart, or whether he had systemic amyloidosis with involvement of several organs making heart transplantation inadvisable.

Amyloidosis is the extracellular deposition of a fibrous protein, amyloid, in one or more sites of the body. Virchow named this protein in 1854 based on its color after staining with iodine and sulfuric acid. The protein has unique ultrastructural, radiograph diffraction, and biochemical characteristics. Amyloid may be deposited locally and in limited amounts in an organ where it has no clinical consequences, or it may involve an organ extensively, causing its dysfunction and thus leading to heart failure, liver failure, renal failure, peripheral neuropathy, extensive skin lesions, and/or vascular insufficiency and even the development of angina pectoris or peripheral claudication. There are multiple clinical and biochemical forms of amyloid classified on the basis of the unique fibrous structure each possesses. A classification scheme presently used to describe amyloidosis is shown in Table 2.

Amyloid is an amorphous eosinophilic, extracellular substance with a rubbery consistency and a waxy pink or gray appearance. With amyloid deposition, organs may enlarge markedly, especially the liver, kidney, spleen, heart, and/or tongue. Amyloid stains pink with hematoxylin and eosin stain and shows metachromasia with crystal violet. The Congo red stain allows amyloid to be identified as a green birefringence when sections are viewed under the polarizing microscope. Electron microscopy allows the amyloid fibril to be identified by its characteristic appearance.

Involvement of the heart by amyloid may be focal or diffuse with amyloid deposits in the myocardium, endocar-
FIG 3. Radiograph of the skull is unremarkable; no lytic lesions are present.

FIG 4. Chest radiograph showing mild hyperexpansion of the lungs suggestive of chronic obstructive pulmonary disease. The heart is normal in size. No focal consolidation is present.
TABLE 2. Classification of Amyloidosis

1. Primary amyloidosis (AL type) with no evidence of preexisting or coexisting disease
2. Amyloidosis associated with multiple myeloma (also AL type)
3. Reactive amyloidosis associated with chronic infectious diseases, such as osteomyelitis, tuberculosis, ulcerative colitis, or other chronic inflammatory disease (AA type)
4. Heretofamilial amyloidosis, neuropathic (AF transthyretin or prealbumin type), and the amyloidosis associated with familial Mediterranean fever (AA type)
5. Local amyloidosis with focal, tumor-like deposits that occur in isolated organs without evidence of systemic involvement
6. Amyloidosis associated with aging, especially in the heart and the brain
7. Amyloidosis associated with long-term hemodialysis
8. Amyloidosis of endocrine tissues (eg, precalcitonin in medullary carcinoma of the thyroid gland)

dium, and/or pericardium. In the aged heart, the atrium usually is involved focally, but there may be more diffuse lesions in both atria and ventricles. Cardiac manifestations consist primarily of congestive heart failure and cardiomegaly with and without murmurs and a variety of arrhythmias and conduction abnormalities. The deposition of amyloid may lead to either a dilated cardiomyopathy with predominant systolic dysfunction and progressive heart failure or slight cardiomegaly with a restrictive physiology, such that diastolic dysfunction is the predominant clinical problem, leading to heart failure. Amyloid involvement of the coronary arteries may cause angina and even myocardial infarction. Involvement of the aortic valve may lead to a systemic murmur, suggesting obstruction of the valve. The pericardium may be involved as well, and although rare, pericardial effusion has been reported. Echocardiographically, symmetric thickening of the left ventricular wall with relatively small ventricular chambers and a characteristic pattern of a diffuse hyperrefractile "granular, sparkling" appearance may be identified. ECG abnormalities include the presence of low-voltage QRS complexes and abnormalities in atrioventricular and intraventricular conduction, often resulting in various degrees of heart block. Atrial arrhythmias are common, especially atrial fibrillation. Radionuclide techniques used to identify the presence of myocardial necrosis, including Tc-pyrophosphate scintigraphy, often demonstrate diffuse myocardial uptake. Infarct or pseudoinfarct patterns may be present on the ECG (Fig 1) as a result of amyloid infiltration of heart muscle causing a "pseudoinfarct" pattern and amyloid involvement of coronary arteries leading to actual myocardial infarction.

In patients who develop heart failure as a consequence of extensive amyloid deposition, the clinical course generally is relentless and progressive to death within a period of approximately 14 months. Initially, salt restriction and the use of diuretics may lead to some symptomatic improvement, but very soon the progressive nature of the process is realized and symptoms progress. The use of digitalis preparations is controversial in patients with amyloidosis. Clearly, they may be
useful in the control of heart rate in patients with atrial fibrillation, and in the early stages of amyloid deposition in heart, they may also provide some symptomatic benefit in the treatment of congestive heart failure. However, once amyloid deposition is extensive, the value of cardiac glycosides is questionable, and they need to be given with care since patients with cardiac amyloidosis may be sensitive to digitalis.

In our patient, a repeat cardiac catheterization and myocardial biopsy were performed at our institution. The patient had evidence of elevated left ventricular end-diastolic pressure and systolic dysfunction without restrictive physiology. His coronary arteries were normal. The repeat myocardial biopsy demonstrated progression of his amyloid deposition.

The remaining key question related to the further evaluation and treatment of this patient was determination of whether the amyloidosis was limited to his heart or whether he had systemic amyloidosis, in which case further consideration of a heart transplant would not be indicated. A bone marrow with biopsy and a rectal biopsy were obtained. His bone marrow demonstrated an increased number of plasma cells, including immature plasma cells, and amyloid deposits, especially perivascular deposits. The rectal biopsy also demonstrated amyloid deposits. A serum protein immunoelectrophoresis demonstrated an increase in immunoglobulin G of the κ type, but we did not demonstrate Bence-Jones proteinuria. A bone scan failed to demonstrate lytic lesions in the skull, pelvis, or long bones.

Thus, the additional evaluations made it clear that our patient had systemic amyloidosis without evidence of multiple myeloma. His heart failure probably was related to the progressive deposition of amyloid. With the identification of systemic amyloidosis, further consideration of heart transplantation became inadvisable. We elected to treat him cautiously with a diuretic, salt restriction, and digoxin and to continue his colchicine therapy. His clinical course was atypical in that the progression in his symptoms had been rather slow, and he was alive and able to perform limited activities approximately 18 months after the diagnosis initially was made. Thus, his systemic amyloidosis was progressing more slowly than is typical of many other individuals.1 Colchicine has been used in patients with familial Mediterranean fever and associated amyloidosis and has been shown to slow the progression of amyloid deposition in such individuals.1 Whether colchicine alters the progression of systemic amyloidosis in patients without familial Mediterranean fever is uncertain presently, but one wonders about its possible protective role in this patient, whose clinical deterioration was progressing more slowly than usual.

Heart transplantation has been used in the treatment of isolated individuals with amyloid deposits limited to their hearts, and prolonged survivals of at least 2 to 3 years without clinical evidence of new heart failure have been described (Dr O.H. Frazier, Case Records of St Luke’s Episcopal Hospital/Texas Heart Institute, Houston, Tex; personal communication, 1993). However, the long-term outcome for such patients is not clear at this time.

Pathological Discussion (L. Maximilian Buja, MD)

I would like to present this case from the point of view of diagnostic pathology. Basically, we were presented

---

FIG 6.  A, Bone marrow section exhibiting arteriole with a hyalinized wall and plasma cells among the hematopoietic cells (hematoxylin and eosin stain). B, Bone marrow smear exhibiting plasma cells with atypical features (Wright-Giemsa stain).
with a 70-year-old man with manifestations of congestive heart failure with angiographically normal coronary arteries and no history of hypertension. This presentation lead to a diagnostic evaluation of possible causes of cardiomyopathy in this patient. As first elucidated by Goodwin, cardiomyopathies may be classified as (1) congestive (dilated), (2) hypertrophic, (3) restrictive, and (4) obliterative.8-13 This is a clinically useful, pathophysiological classification with etiological implications. The least common, obliterative type is the typical pattern produced by hypereosinophilic syndromes. Hypertrophic cardiomyopathy usually is an inherited disorder with characteristic pathophysiological manifestations, although a similar phenotype occasionally can present on an acquired basis or in association with other diseases. The most common type, congestive cardiomyopathy, is usually acquired due to viral infection, chronic alcoholism, or other causes, although it may be familial. The restrictive type of cardiomyopathy occurs less frequently than the congestive type. The most common, known cause of restrictive cardiomyopathy is amyloid, but there are other nonamyloidotic forms of restrictive cardiomyopathy.5 Amyloid can also be associated with a congestive type of cardiomyopathy.

The first step was to review this patient’s myocardial biopsy obtained 18 months previously at another institution. The biopsy revealed evidence of focal amyloid deposition in one small artery and adjacent interstitium. This was based on the presence of homogeneous hyaline material replacing the wall of the blood vessel. This material had characteristic tinctorial properties, including a grayish-blue color on Masson trichrome stain and red color on Congo red stain with apple-green birefringence under polarized light (Fig 5). This biopsy was taken 18 months before the patient presented to us, and he presented here with relatively mild cardiac dysfunction. This indolent course is unusual for the evolution of amyloid heart disease. Thus, the considerations quickly switched from documenting the presence of amyloid to determining the extent, type, and significance of the amyloid.

Amyloid was originally characterized by Rudolf Virchow in the mid-1850s and named by him “starchlike” based on a gross histochemical reaction with iodine and sulfuric acid yielding a blue color, a reaction similar to that given by starches and related carbohydrates. We now know that the term “amyloid” is a misnomer because extensive research has documented that amyloid is a generic category of proteins with the unifying property that all of the amyloid proteins have the same secondary conformation, which is known as a β-pleated-sheet conformation, even though the primary amino acid compositions of the proteins differ according to the specific type of amyloid. This conformation is different from most biological proteins, which have an α helical conformation. It is the β-pleated-sheet conformation that is responsible for the characteristic type of binding of aniline dyes, including Congo red, to amyloid to produce the apple-green birefringence on polarization microscopy as well as the other diagnostic criteria for amyloid. These include homogeneous hyaline material on light microscopic examination that is eosinophilic in hematoxylin and eosin stain and grayish-blue in Masson trichrome stain; Congo red positivity with apple-green birefringence with polarized light; characteristic non-branching 10-nm fibrils, with or without ring-shaped p-component by electron microscopy; and characteristic x-ray diffraction pattern of a β-pleated-sheet conformation of the protein. Thus, proteins with different amino acid sequences and immunological and biological features are identifiable as types of amyloid based on shared physicochemical properties. The experimental pathologist George Glenner and the rheumatologist Alan Cohen have provided important insights into the modern basis of understanding of amyloid.14,15

Thus, the amyloid diseases are based on the type of amyloid protein involved (Table 2). These proteins include AL amyloid, composed of immunoglobulin light-chain fragments and related to immunological and neoplastic diseases; AA amyloid, composed of a product of a protein (SAA) synthesized in the liver in various autoimmune states and infections; transthyretin or prealbumin associated with senile amyloidosis and isolated cardiac involvement and other conditions; the endocrine amyloids; and amyloid associated with Alzheimer's disease.1 Given the facts of the case, the main differential diagnosis in this patient was whether he had the AL type of amyloid or whether he had the prealbumin (transthyretin) type of amyloid, which is associated with isolated cardiac amyloidosis or localized senile amyloidosis. Other considerations were whether the patient had some type of idiopathic cardiomyopathy, with incidental amyloid in the heart related to his age, or whether amyloid deposition was the basis for his heart disease. Did he have amyloid in locations other than the heart? Did he have multiple myeloma?
Based on these considerations, we performed a bone marrow examination, which showed that the patient had a normocellular marrow with 20% plasma cells, some of which had atypical features (Fig 6). Thus, the bone marrow had a moderate plasmacytosis but was not diagnostic of multiple myeloma. Congo red stain on the bone marrow was reported as negative. The Congo red stain is touted as providing definitive diagnostic information regarding amyloidosis, but it is a difficult stain to perform and interpret. It can be falsely negative when there are only small amounts of amyloid. It is always important to couple the histochemistry with electron microscopy.

Based on the initial report on the bone marrow, biopsies were performed of gingiva, abdominal skin and fat, and rectum. On Congo red stain, the gingival biopsy was negative, but the abdominal skin biopsy had many of the sweat glands and small blood vessels with Congo red-positive material in the basement membranes (Fig 7). These areas showed the characteristic apple-green birefringence of amyloid in contrast to collagen, which has a white birefringence. The rectal biopsy also was positive for amyloid.

On reexamination of the bone marrow, some blood vessels in the bone marrow were identified with hyalinized eosinophilic material in their walls (Fig 6). On electron microscopy examination, a blood vessel showed deposition of matted fibrillar material, which at high magnification had the composition of nonbranching fibrils of about 10 nm (100 Å) in diameter (Figs 8 and 9). These fibrils were typical of amyloid.

The repeat myocardial biopsy showed multifocal hyaline deposits in the interstitium as well as in blood vessels (Fig 10). This material stained positively with Congo red had positive apple-green birefringence and consisted of tangled masses of small filaments by electron microscopy. In this myocardial biopsy, electron microscopy showed a thin rim of amyloid surrounding several myocytes (Figs 11 and 12). The perivascular and interstitial amyloid deposition predisposes to impaired oxygen transport to the muscle cells and eventual ischemic atrophy and loss of myocytes.

To summarize, 18 months before admission, there was evidence of limited vascular amyloid deposits in the heart. The new diagnostic evaluation revealed evidence of systemic amyloid deposition. The bone marrow had 20% plasma cells, and electron microscopy showed amyloid fibrils in a blood vessel. Gingival biopsies were negative; however, rectal and abdominal fat biopsies were positive, and there was evidence of progression of amyloid involvement of the heart.

Immunocytochemistry also was performed on the second heart biopsy. A good antibody to the AA-type amyloid was available for paraffin sections. Staining for AA amyloid was negative. However, our antibodies for k and light chains were not ideally suited for paraffin sections, and the results were equivocal. Permanganate staining also was equivocal. In retrospect, it would have been helpful to freeze some of the biopsy since k and A immunocytochemistry is much better in frozen sections than in the paraffin sections.

Nevertheless, the evaluation suggested the AL type of amyloid with systemic involvement, unfortunately,
rather than the prealbumin type with localized cardiac involvement. We sought help in the diagnosis by turning to analysis of the serum and urine by the Clinical Immunology Laboratory. Dr Hartwell presents these findings.

Immunochemical Analysis (Dr Elizabeth Hartwell)

Protein electrophoresis was performed on serum and urine samples from the patient. Serum protein electrophoresis showed a normal distribution of all globulin fractions with a small restricted band in the mid-gamma region, corresponding to a monoclonal protein. Protein electrophoresis on a random urine sample (total protein, 7 mg/dL) showed no abnormalities.

Serum immunofixation electrophoresis was performed to characterize the monoclonal protein present. Immunofixation electrophoresis is agarose gel electrophoresis followed by immunoprecipitation through the direct application of monospecific antisera (anti-immunoglobulin G, A, and M and anti-κ and -λ) to the gel. Analysis of the immunofixation electrophoresis gel (Fig 13) showed a restricted dense band in the lane containing anti-immunoglobulin G antiserum with a band of corresponding mobility in the lane containing anti-κ antiserum. This identified the monoclonal serum protein as immunoglobulin G-κ. In addition, migrating in a slightly anodal position, a second, very faint monoclonal immunoglobulin G-κ protein was detected.

Although a monoclonal band was not seen on routine urine protein electrophoresis, immunofixation electrophoresis was performed to detect monoclonal immunoglobulins that may have been present in the urine at low concentrations. The immunofixation electrophoresis gel (Fig 14) showed at least four discrete, evenly spaced bands present in the κ lane without corresponding bands in any of the heavy-chain lanes. The significance of these multiple bands was uncertain. This type of light-chain pattern has been called a "ladder," "stair-step," or "pseudo-oligoclonal" pattern, which is thought to be due to the presence of free polyclonal light chains in the urine. Although the ladder light-chain pattern is most likely of limited clinical significance, it can mask co-migrating monoclonal light chains (Bence-Jones protein) present at a low concentration. Therefore, the urine immunofixation study in this patient was inconclusive and should have been repeated on a 24-hour urine sample. Further analysis by immunoblotting could also have been performed to determine if free monoclonal κ light chains are present.

In this patient, the presence of 20% plasma cells in a bone marrow aspirate and a monoclonal protein in the serum raises the possibility of multiple myeloma. Quantitative serum immunoglobulin levels in the patient were as follows: immunoglobulin G, 1520 mg/dL (reference range [RR], 800 to 1800); immunoglobulin M, 250 mg/dL (RR, 60 to 250); and immunoglobulin A, 211 mg/dL (RR, 90 to 450). This corresponded with the lack of background suppression of immunoglobulins seen on the serum protein electrophoresis. In malignant monoclonal gammopathies, such as multiple myeloma, the levels of the uninvolved (or normal, polyclonal) immunoglobulins often are depressed. This was not the case with our patient.
FIG 10. Second myocardial biopsy exhibiting prominent accumulations of amorphous material in the myocardial interstitium and perivascular regions (Masson trichrome stains).

FIG 11. Low-magnification electron micrograph of myocardium showing masses of fibrillar material in the interstitium surrounding cardiac myocytes. ×5000.
Studies performed at the Mayo Clinic demonstrated the presence of a monoclonal protein in the serum and/or urine in more than 80% of patients with primary systemic amyloidosis. In the majority of their patients, the monoclonal protein band was unimpressive with a serum monoclonal protein level of 1 g/dL or less. In this patient, the monoclonal protein accounted for approximately 0.5 g/dL of the total serum protein. Although \( \lambda \) light chains characteristically are associated with amyloidosis, of patients with primary systemic amyloidosis and a monoclonal serum protein, 17% had an immunoglobulin G–\( \kappa \) monoclonal immunoglobulin.

**Dr Buja**

I think that the immunochemistry was very helpful in this case. According to the various criteria used for the diagnosis of plasma cell myeloma, such as those put forward by the Southwest Oncology Group, the patient...
does not have diagnostic criteria for multiple myeloma. Therefore, I think that the patient has a disease that is part of the spectrum of plasma cell or immunocyte dyscrasia, which includes primary systemic amyloidosis, multiple myeloma with amyloid deposition, and multiple myeloma alone. The diagnostic evaluation indicated that our patient had primary systemic amyloidosis.

As Dr Willerson pointed out, in all the various kinds of amyloidosis, the basic pathogenesis involves a stimulus, known or unknown, that produces a soluble precursor. Localized or limited proteolysis of the material in the tissue then leads to the deposition of an insoluble, β-pleated-sheet fibril resulting in amyloidosis. The prognosis for these patients with manifestations of orthostatic hypotension or congestive heart failure is very poor. Thus, I think our patient is an unusual case of AL amyloidosis with a protracted clinical course despite progressive cardiac involvement over 18 months.

References

Key Words • Clinicopathological Conference • heart failure • amyloidosis
Congestive heart failure in a 70-year-old man.
J T Willerson, P C Chen, E A Hartwell and L M Buja

Circulation. 1993;88:1336-1347
doi: 10.1161/01.CIR.88.3.1336

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/88/3/1336.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/