

Amyloidosis

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The word *amyloid* was first coined in 1838 by Schleiden, a German botanist, to describe a normal constituent of plants. Virchow [1] observed the similarity of the staining properties of the amyloid to those of starch and named it amyloid.

All forms of amyloid appear homogeneous when viewed under a light microscope and are pale pink when stained with hematoxylin-eosin. Under polarized light, amyloid stained with Congo red dye produces the characteristic apple-green birefringence. The modification of alkaline Congo red dye by Puchtler and Sweat [2] is used most often. The amorphous hyaline-like appearance of amyloid is misleading because it is a fibrous protein. On electron microscopy, amyloid deposits are composed of rigid, linear, non-branching fibrils 7.5- to 10-nm wide and of indefinite length. The fibrils aggregate into bundles. The deposits occur extracellularly and ultimately lead to damage of normal tissue.

In primary amyloidosis (AL) the fibrils consist of the variable portions of monoclonal (κ) or (λ) immunoglobulin light chains or, very rarely, heavy chains. In secondary amyloidosis (AA) the fibrils consist of protein A, a non-immunoglobulin. In familial amyloidosis (AF) the fibrils are composed of mutant transthyretin (prealbumin) or, rarely, fibrinogen or apolipoprotein. In senile systemic amyloidosis the fibrils consist of normal transthyretin. The amyloid fibrils associated with long-term dialysis (A β_2 M dialysis arthropathy) consist of β_2 -microglobulin.

Amyloid P component is a glycoprotein composed of 10 identical glycosylated polypeptide subunits, each with a molecular weight of 23,500 and arranged as two pentamers. The liver produces human serum amyloid P (SAP) component. SAP is present in healthy persons and shows 50% to 60% homology with C-reactive protein. SAP is bound to the amyloid fibrils; it is not an integral part of the fibrillar structure. It is found in all types of amyloid, including the vessel walls in patients with Alzheimer's disease. The physiologic function of SAP and its pathologic role in amyloidosis are unknown. Glycosaminoglycans are present in amyloid deposits. Their role also is unknown. Catabolism or breakdown of the fibrils is an important factor in pathogenesis; however, little is known of the process [3].

No obvious predisposing condition is associated with primary amyloidosis. Secondary amyloidosis is associated with an inflammatory process, malignancy, and many other conditions. No monoclonal protein exits in the serum or urine.

CHAPTER

3

Microscopic Appearance and Classification

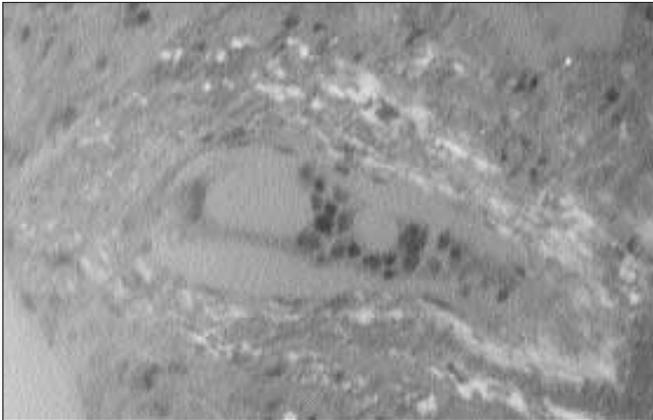


FIGURE 3-1 (see Color Plate)

Blood vessel from a bone marrow biopsy specimen indicating primary amyloidosis. The specimen was stained with Congo red dye and viewed with a polarizing light source, producing the characteristic apple-green birefringence. In more than half of patients, results of bone marrow testing are positive for amyloidosis. (From Kyle [4]; with permission.)

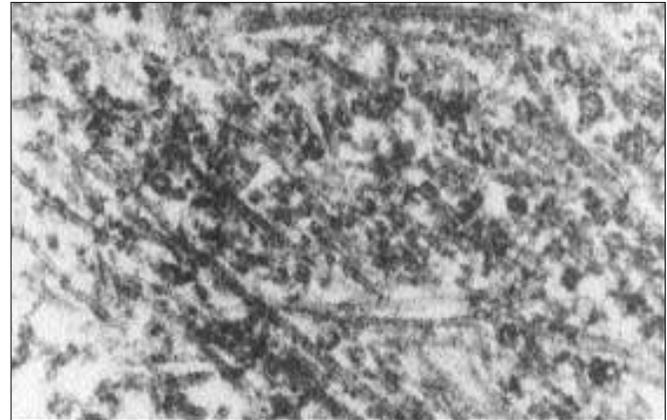


FIGURE 3-2

Electron photomicrograph showing the fibrillar character of amyloidosis. The fibrils are 7.5- to 10-nm wide and of indefinite length. The fibrils are deposited extracellularly, are insoluble, and generally resist proteolytic digestion. They ultimately lead to disorganization of tissue architecture and loss of normal tissue elements.

CLASSIFICATION OF AMYLOIDOSIS

Amyloid type	Classification	Major protein component
Primary amyloidosis (AL)	Primary, including multiple myeloma	κ or λ light chain
Secondary amyloidosis (AA)	Secondary	Protein A
Familial amyloidosis (AF)	Familial	
	Neuropathic: Portugal, Sweden, Japan, and other countries	Transthyretin mutant (prealbumin)
	Cardiopathic: Denmark and Appalachia in the United States	Transthyretin mutant (prealbumin)
	Nephropathic: familial Mediterranean fever	Protein A
Senile systemic amyloidosis (AS)	Senile cardiac	Transthyretin normal (prealbumin)
Dialysis amyloidosis (AD)	Dialysis arthropathy	β_2 -microglobulin

FIGURE 3-3

Classification of amyloidosis. The fibrils in primary amyloidosis consist of monoclonal κ or λ light chains. Rarely, monoclonal heavy chains are responsible. The major component of the amyloid fibril in secondary amyloidosis is protein A. It has a molecular weight of 8.5 kD

and contains 76 amino acids. It is derived from serum amyloid A, which is an acute-phase protein. The level of serum amyloid A is increased in patients with rheumatoid arthritis and Crohn's disease. In familial amyloidosis the Portuguese, Swedish, and Japanese variants are characterized by substitution of methionine for valine at residue 30 (Met-30) in the transthyretin molecule. This mutation is characterized by the development of peripheral neuropathy. Cardiomyopathy from a transthyretin mutation has been reported in Denmark (Met-111) and in the Appalachian area of the United States (Ala-60). Familial renal amyloid from a mutation of the fibrinogen α -chain (Leu-554 or Glu-526) or mutations of lysozyme have been reported. Amyloidosis associated with familial Mediterranean fever consists of protein A. Senile systemic amyloidosis involving the heart results from the deposition of normal transthyretin. Long-term dialysis often results in systemic amyloidosis from β_2 -microglobulin deposition.

SYSTEMIC AMYLOIDOSIS

Amyloid type	Amyloid stains				
	Congo red	κ or λ	Serum amyloid A	β_2 -microglobulin	Transthyretin (prealbumin)
Primary (AL)	+	+	-	-	-
Secondary (AA)	+	-	+	-	-
FMF	+	-	+	-	-
Associated with long-term hemodialysis	+	-	-	+	-
Familial (AF)	+	-	-	-	+
Senile systemic (AS)	+	-	-	-	+

FIGURE 3-4

Systemic amyloidosis. Types of proteins constituting the amyloid fibrils. In primary amyloidosis the fibrils consist of monoclonal κ or λ light chains. In secondary amyloidosis the fibrils consist of protein A. Systemic amyloidosis associated with long-term hemodialysis consists

of β_2 -microglobulin. The amyloid fibrils consist of mutated transthyretin or, rarely, fibrinogen α or lysozyme in familial amyloidosis. Senile systemic amyloidosis is characterized by the deposition of normal transthyretin in the heart. (From Kyle and Gertz [5]; with permission.)

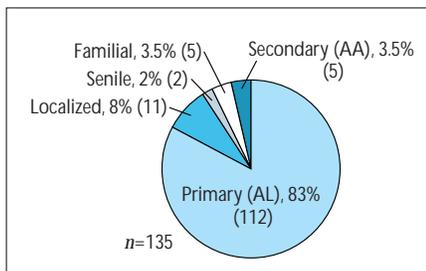


FIGURE 3-5

Distribution of forms of amyloidosis seen in patients at the Mayo Clinic in 1996. Of the 135 patients with amyloidosis, 83% had the primary form. Familial, secondary, and senile amyloidosis accounted for less than 10% of patients. Localized amyloid is limited to the involved organ and never becomes systemic. In localized amyloidosis, the fibrils consist of an immunoglobulin light chain; however, the patients do not have a monoclonal protein in their serum or urine. Most localized amyloidosis occurs in the respiratory tract, genitourinary tract, or skin.

Primary Systemic Amyloidosis

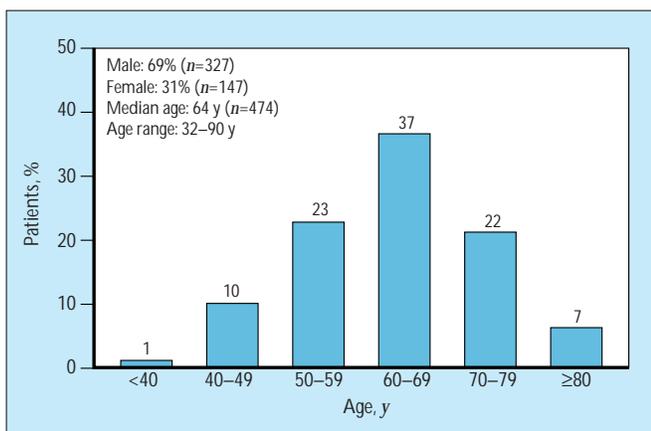
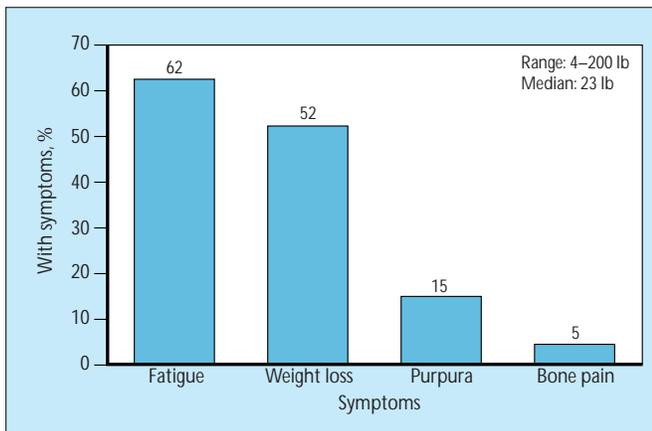


FIGURE 3-6

Pattern of primary systemic amyloidosis in patients during an 11-year study at the Mayo Clinic. From 1981 to 1992, of the 474 patients seen within 30 days of diagnosis the median age was 64 years. Only 1% were younger than 40 years, and males were affected more often than were females. (From Kyle and Gertz [5]; with permission.)

**FIGURE 3-7**

Symptoms of primary systemic amyloidosis in patients during an 11-year study at the Mayo Clinic. Weakness or fatigue and weight loss were the most frequent initial symptoms seen within 30 days of diagnosis. Weight loss occurred in more than half of patients. The median weight loss was 23 lb; five patients lost more than 100 lb each. Purpura, particularly in the periorbital and facial areas, was noted in about one sixth of patients. Gross bleeding was reported initially in only 3%. Skeletal pain was a major symptom in only 5% and usually was related to lytic lesions or fractures associated with multiple myeloma. Dyspnea, pedal edema, paresthesias, light-headedness, and syncope were noted. (From Kyle and Gertz [5]; with permission.)

**FIGURE 3-8**

Macroglossia in a man with primary systemic amyloidosis. Macroglossia occurs initially in about 10% of patients. Note the imprint of the teeth on the dorsum of the tongue. This patient was unable to close his mouth and complained of drooling. Macroglossia may cause obstruction of the airway, sometimes necessitating a tracheostomy. (From Kyle [4]; with permission.)

**FIGURE 3-9**

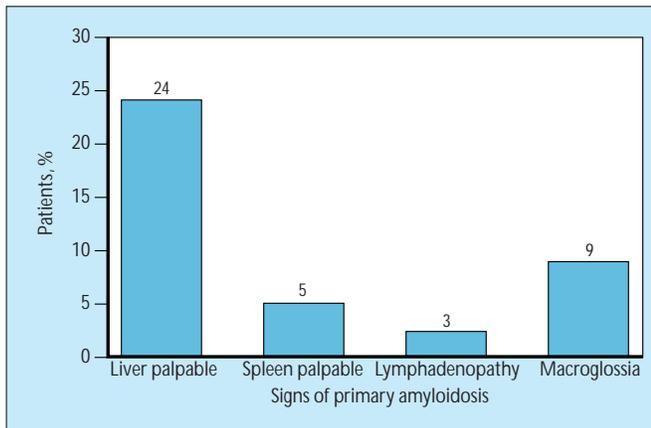
Nodules causing occlusion of the auditory canal in a patient with primary systemic amyloidosis. The external auditory canal may be occluded completely by nodules of amyloid. This condition frequently produces deafness, which may be the initial symptom. (From Gertz and Kyle [6]; with permission.)

**FIGURE 3-10**

Shoulder pad sign in a woman with primary systemic amyloidosis. Infiltration of the periarticular tissues with amyloid may produce this sign. The shoulder pad sign causes pain and limitation of motion and is very difficult to treat. (From Kyle [4]; with permission.)

**FIGURE 3-11**

Hypertrophic form of primary systemic amyloidosis in a 39-year-old man with prominent and firm muscles. Despite the muscular appearance, results of a biopsy revealed displacement of muscle fibers with amyloid. Patients often exhibit stiffness or limitation of movement. (From Kyle and Greipp [7]; with permission.)

**FIGURE 3-12**

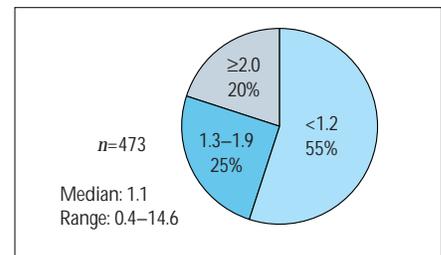
Signs of primary systemic amyloidosis in patients during an 11-year study at the Mayo Clinic. The liver was palpable in about one fourth of patients seen within 30 days of diagnosis. Hepatomegaly is due to infiltration of amyloid or congestion from heart failure. The spleen is palpable in only 5% of patients and rarely extends more than 5 cm below the left costal margin. Lymphadenopathy occurs infrequently. (Adapted from Kyle and Gertz [5]; with permission.)

HEMOGLOBIN AND PLATELET VALUES WITHIN 30 DAYS OF DIAGNOSIS OF PRIMARY SYSTEMIC AMYLOIDOSIS, MAYO CLINIC, 1981–1992

Factor	Median	Range
Hemoglobin, g/dL (<10 g/dL in 11%)	12.9	6.6–18.6
Platelets, $\times 10^9/L$ (> $500 \times 10^9/L$ in 9%)	288	4–953

FIGURE 3-13

Hemoglobin and platelet values within 30 days of diagnosis of primary systemic amyloidosis. Anemia was not a prominent feature. When present, it usually is due to multiple myeloma, renal insufficiency, or gastrointestinal bleeding. Thrombocytosis was relatively common; in 9% of patients the platelet count was over $500 \times 10^9/L$. Functional hyposplenism from amyloid replacement of the spleen may occur [8]. Hyposplenism is manifested by the presence of Howell-Jolly bodies and occurs in about one fourth of patients. (Adapted from Kyle and Gertz [5].)

**FIGURE 3-14**

Serum creatinine (mg/dL) in patients at diagnosis of primary systemic amyloidosis. Renal insufficiency was present in almost half of patients. Proteinuria was present in about 75% of patients.

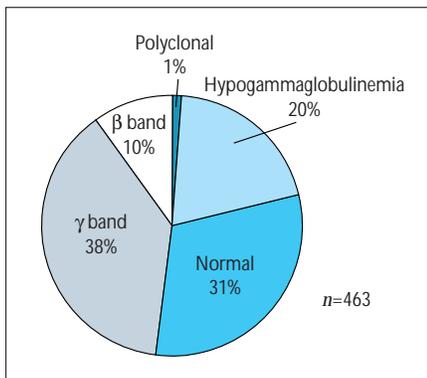


FIGURE 3-15

Results of serum protein electrophoresis in patients at diagnosis of primary systemic amyloidosis. The serum protein electrophoretic pattern showed hypogammaglobulinemia in 20% of patients. Only half of patients had a localized band or spike in the β or γ areas of the electrophoretic pattern. The median size of the M spike was 1.4 g/dL. In the remaining patients the pattern was normal.

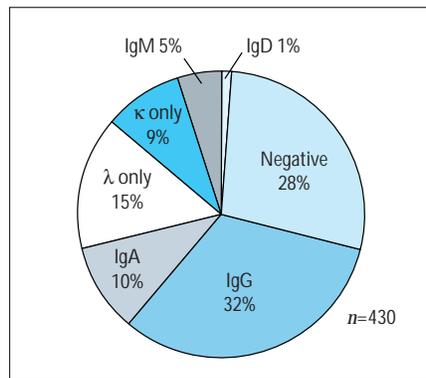


FIGURE 3-16

Serum monoclonal (M-) protein in patients at diagnosis of primary systemic amyloidosis in an 11-year study at the Mayo Clinic. Immunoelectrophoresis or immunofixation of the serum showed an M-protein in 72% of patients. IgG was most common, followed by IgA. Twenty-four percent of patients had monoclonal immunoglobulin light chains in the serum (Bence Jones proteinemia). (Adapted from Kyle and Gertz [5]; with permission.)

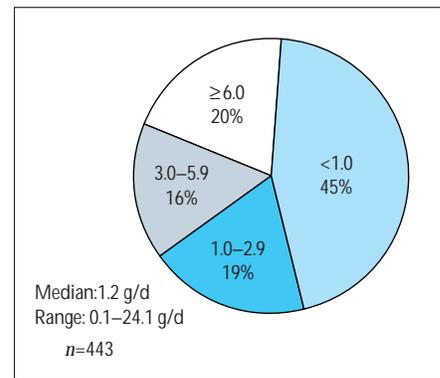


FIGURE 3-17

Urine total protein values in patients at diagnosis of primary systemic amyloidosis in an 11-year study at the Mayo Clinic. More than one third of patients exhibited 24-hour urine total protein values of 3.0 g/d or more. Over half of patients had a urine protein value of more than 1 g/d. The electrophoretic pattern showed mainly albumin. (Adapted from Kyle and Gertz [5]; with permission.)

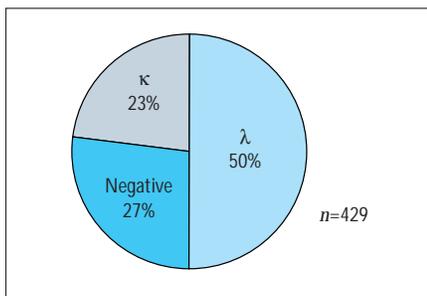


FIGURE 3-18

Urine monoclonal (M-) protein in patients at diagnosis of primary systemic amyloidosis in an 11-year study at the Mayo Clinic. Almost three fourths of patients had monoclonal light chains in their urine on immunoelectrophoresis or immunofixation. In contrast to the type of protein found in multiple myeloma, λ is twice as common as is κ . The 24-hour total amount of monoclonal (M-) protein in the urine was less than 0.5 g/d in more than half of patients. (From Kyle and Gertz [5]; with permission.)

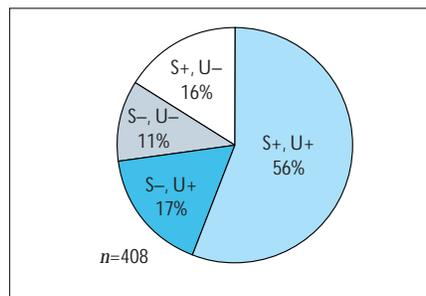


FIGURE 3-19

Serum (S) and urine (U) proteins in patients with primary systemic amyloidosis in an 11-year study at the Mayo Clinic. Immunoelectrophoresis or immunofixation of serum and appropriate concentrations in urine showed a monoclonal protein in nearly 90% of patients. In the absence of monoclonal protein, one must search for a monoclonal population of plasma cells in the bone marrow or perform immunohistochemical staining to identify the type of amyloid. (From Kyle and Gertz [5]; with permission.)



FIGURE 3-20

Enlarged kidney in primary systemic amyloidosis. Involvement of the kidneys is the most common presenting feature. The kidney is frequently normal in size, but in some instances small kidneys have been found.

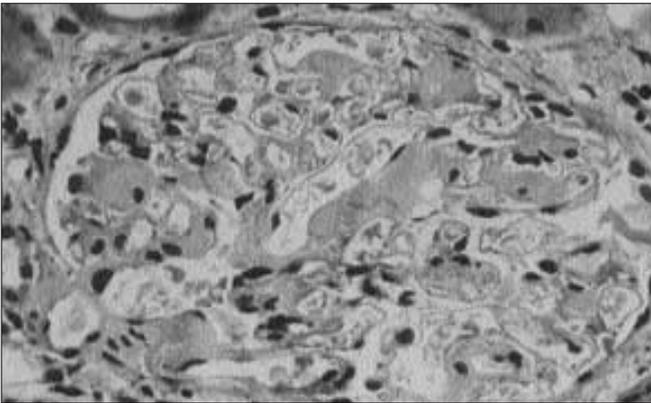


FIGURE 3-21 (see Color Plate)

Photomicrograph showing a renal biopsy specimen stained with Congo red dye taken from a patient with primary systemic amyloidosis. Note the homogeneous deposition of amyloid in the glomerulus. Results of kidney biopsy are positive in about 95% of patients.

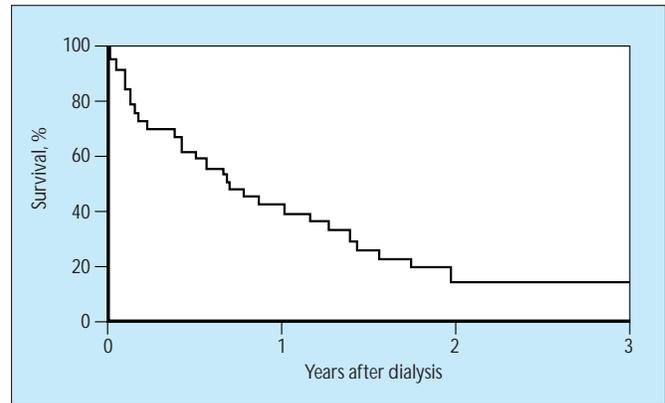


FIGURE 3-22

Survival analysis of patients with primary systemic amyloidosis. The median survival from the onset of dialysis was 8.2 months in 37 patients. No difference exists between patients treated with hemodialysis and those treated with peritoneal dialysis. Biopsy results were used to make the diagnosis in 211 patients. The most important predictors of which patients would ultimately require dialysis were the 24-hour urinary protein loss and serum creatinine values at the time of diagnosis. None of the patients who had a normal serum creatinine value and a urine protein value of less than 2 g/d at diagnosis required dialysis during follow-up. Of the 37 patients who received dialysis, 31 died, and 21 of the 31 died as a result of extrarenal progression of their systemic amyloidosis. Half of the deaths were caused by cardiac amyloidosis [9].



FIGURE 3-23

Gross specimen of a liver in primary systemic amyloidosis. The liver is grossly enlarged.

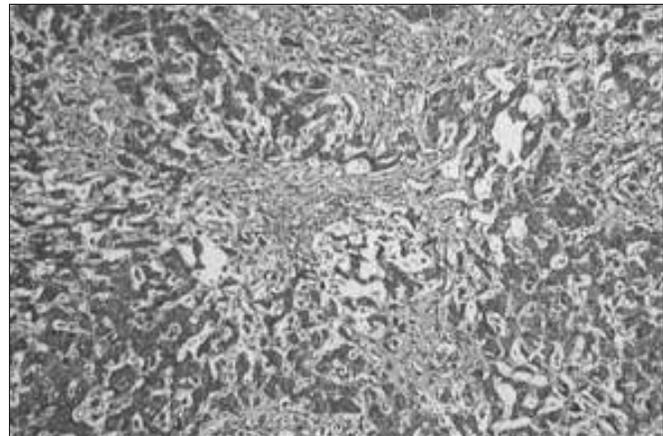


FIGURE 3-24

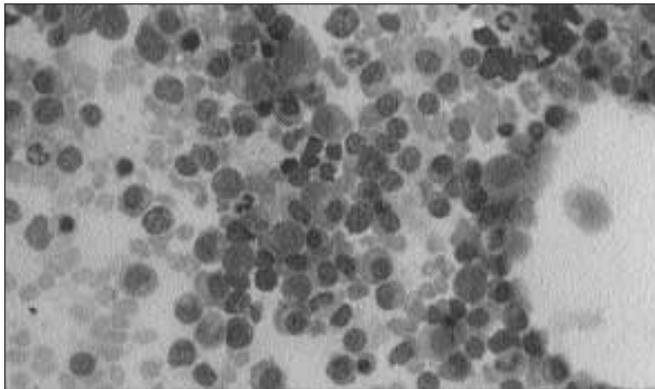
Photomicrograph showing extensive amyloid deposition in the liver in primary systemic amyloidosis.

ALKALINE PHOSPHATASE, ASPARTATE AMINOTRANSFERASE, AND BILIRUBIN VALUES WITHIN 30 DAYS OF DIAGNOSIS OF PRIMARY SYSTEMIC AMYLOIDOSIS, MAYO CLINIC, 1981–1992

Factor	Normal value	Values above normal, n (%)
Alkaline phosphatase	≤250 U/L	>250 (26) ≥500 (11)
Aspartate aminotransferase	≤30 U/L	>30 (34) ≥100 (3)
Total bilirubin	≤1.1 mg/dL	>1.1 (11) ≥5 (1)

FIGURE 3-25

Alkaline phosphatase, aspartate aminotransferase, and bilirubin values within 30 days of diagnosis of primary systemic amyloidosis. The serum alkaline phosphatase level was increased in one fourth of 474 patients at the time of diagnosis. The aspartate aminotransferase value was increased in one third of patients but rarely reached 100 U/L. Hyperbilirubinemia was an infrequent finding but when present was associated with short survival [5]. (Adapted from Kyle and Gertz [5].)


FIGURE 3-27

Bone marrow aspirate specimen from a patient with primary systemic amyloidosis. This specimen contains an increase in plasma cells.

PROTHROMBIN TIME, CAROTENE, AND B₁₂ VALUES WITHIN 30 DAYS OF DIAGNOSIS OF PRIMARY SYSTEMIC AMYLOIDOSIS, MAYO CLINIC, 1981–1992

Factor	Patients, %
Prothrombin time >13 s	16
Carotene <48 µg/dL	6
Serum B ₁₂ <150 pg/mL	3

FIGURE 3-26

Prothrombin time, carotene, and vitamin B₁₂ values within 30 days of diagnosis of primary systemic amyloidosis. The prothrombin time was increased in one sixth of patients at the time of diagnosis. It has been shown that prolongation of thrombin time occurs in 40% of patients [10]. A deficiency in factor X occurs in 15% but is not associated with bleeding. Malabsorption as manifested by a low carotene or serum B₁₂ level occurs infrequently. (Adapted from Kyle and Gertz [5].)

PERCENTAGE OF BONE MARROW PLASMA CELLS WITHIN 30 DAYS OF DIAGNOSIS OF PRIMARY SYSTEMIC AMYLOIDOSIS, MAYO CLINIC, 1981–1992

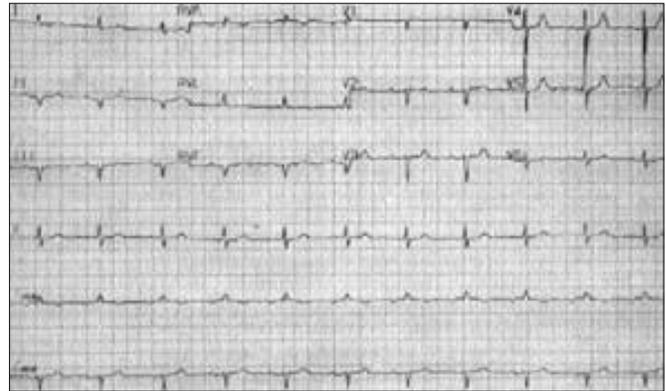
Plasma cells, % (median = 7%)	Patients, % (n = 391)
≤5	44
6–9	16
10–19	22
≥20	18

FIGURE 3-28

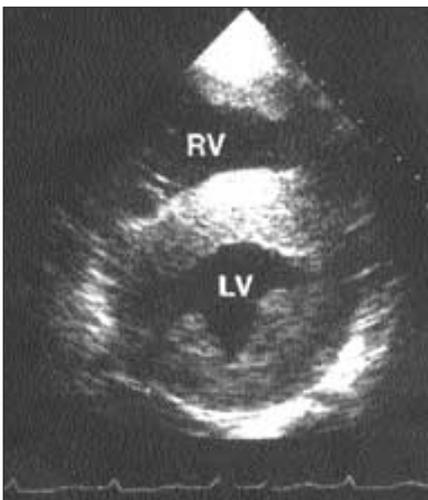
Percentage of bone marrow plasma cells within 30 days of diagnosis of primary systemic amyloidosis. Almost half of patients had 5% or fewer plasma cells in the bone marrow at the time of diagnosis. About one fifth of patients had bone marrow plasmacytosis of 20% or more. Multiple myeloma must be considered in this setting. The plasma cells are monoclonal κ or λ. (From Kyle and Gertz [5]; with permission.)

**FIGURE 3-29**

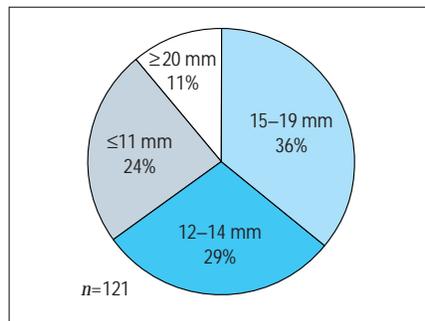
Radiograph showing marked cardiac enlargement in a patient with primary systemic amyloidosis. Overt congestive heart failure is present in about one sixth of patients at the time of diagnosis. Pleural effusion is common.

**FIGURE 3-30**

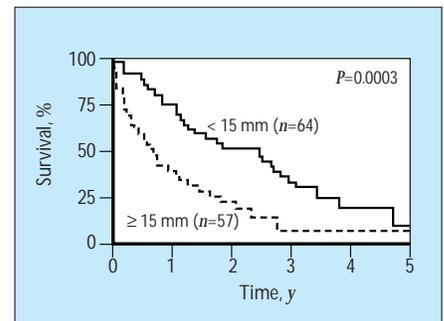
Electrocardiogram in a patient with primary systemic amyloidosis, showing low voltage in the limb leads or loss of anterior septal forces that mimics the findings in myocardial infarction. However, ischemic heart disease is not present. Arrhythmias may include atrial fibrillation, junctional tachycardia, premature ventricular complexes, or heart block.

**FIGURE 3-31**

Echocardiogram of a patient with primary systemic amyloidosis showing marked thickness of the ventricular wall. Results on echocardiogram are abnormal in two thirds of patients at the time of diagnosis. LV—left ventricle; RV—right ventricle. (From Gertz and Kyle [3]; with permission.)

**FIGURE 3-32**

Septal thickness on echocardiography in patients with primary systemic amyloidosis. Almost half of patients had septal thickness of 15 mm or more on echocardiography at the time of diagnosis. Only 24% had no increased septal thickness.

**FIGURE 3-33**

Analysis of the association between septal thickness and survival in patients with primary systemic amyloidosis in an 11-year study at the Mayo Clinic. An increase in septal thickness is associated with shorter survival. Patients with a septal thickness of 15 mm or more had a median survival of 7 months, whereas in those with a septal thickness less than 15 mm the median survival was 26 months. (From Kyle and Gertz [5]; with permission.)

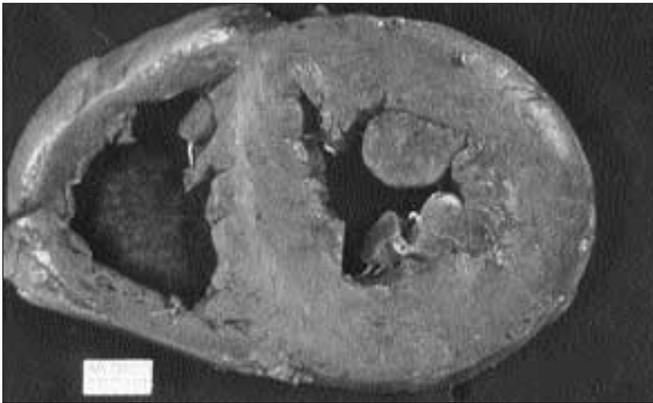


FIGURE 3-34

Cross section of the heart showing marked thickening of the left ventricular wall and septum in primary systemic amyloidosis. The ventricular cavity is greatly reduced in volume. (From Gertz and Kyle [3]; with permission.)

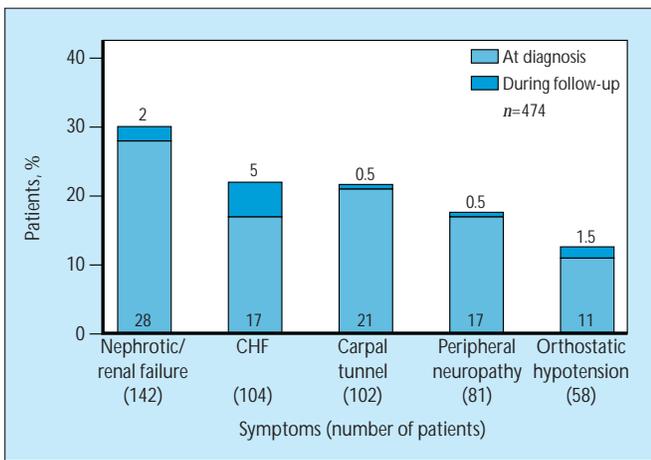


FIGURE 3-35

Analysis of previously unexplained syndromes in patients with primary systemic amyloidosis at the time of diagnosis in an 11-year study at the Mayo Clinic. Nephrotic syndrome or renal failure was present in 28% of patients, congestive heart failure (CHF) in 17%, and carpal tunnel syndrome in 21%. Peripheral neuropathy and orthostatic hypotension also were common features. The possibility of primary systemic amyloidosis must be considered in every patient who has monoclonal protein in the serum or urine and who has unexplained nephrotic syndrome, CHF, sensorimotor peripheral neuropathy, carpal tunnel syndrome, hepatomegaly, or malabsorption. (Adapted from Kyle and Gertz [5]; with permission.)

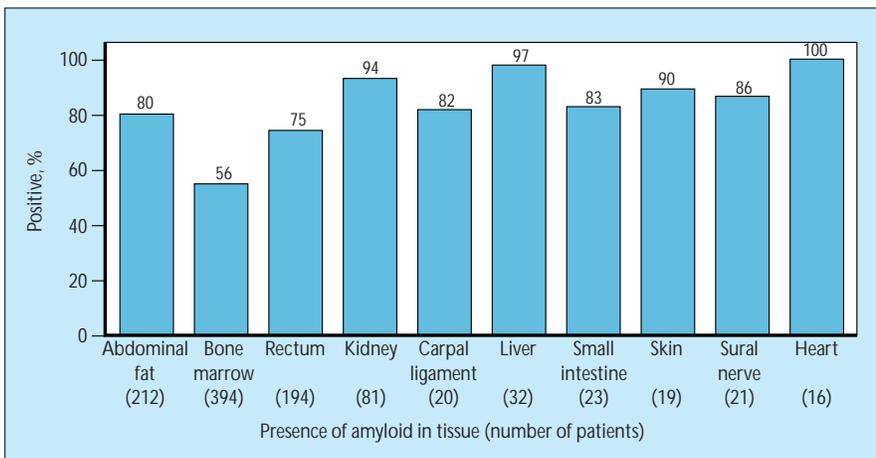


FIGURE 3-36

Diagnosis of primary systemic amyloidosis based on the presence of amyloid in tissue in an 11-year study at the Mayo Clinic. The initial diagnostic procedure should be an abdominal fat aspirate [11]. The diagnosis will be confirmed in 80% of patients. Experience in the staining technique and interpretation of the fat aspirate is important before routine use. A bone marrow aspirate and bone marrow biopsy specimen should be obtained to determine the degree of plasmacytosis, and results of amyloid stains are positive in more than half of patients. Either the abdominal fat aspirate or bone marrow biopsy specimen is positive in 90% of patients. When amyloid is still suspected and the test results of these tissues are negative, one should proceed to performing a rectal biopsy, which is positive in approximately 80% of patients. The specimen must include the submucosa. When the test results for these sites are negative, tissue should be obtained from an organ with suspected involvement. (From Kyle and Gertz [5]; with permission.)

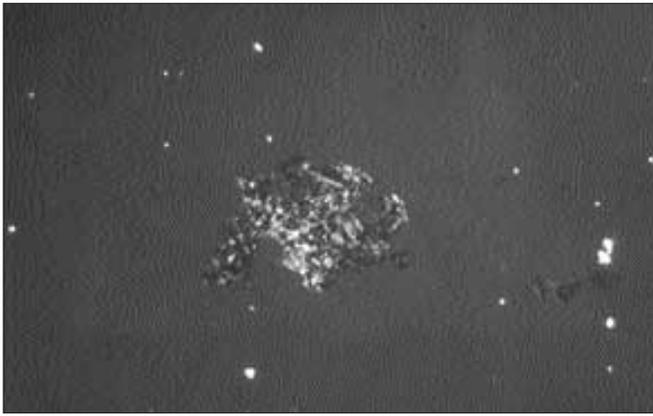


FIGURE 3-37 (see Color Plate)

Aspirate of subcutaneous abdominal fat from a patient with primary systemic amyloidosis. The specimen shows the characteristic apple-green birefringence when stained with Congo red dye and viewed with a polarizing light source.

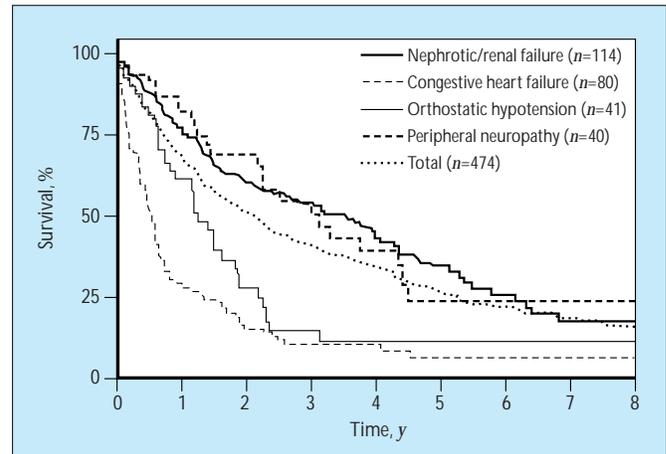


FIGURE 3-38

Analysis of median survival in patients with primary systemic amyloidosis in an 11-year study at the Mayo Clinic. The median survival of 474 patients seen within 1 month of diagnosis was 13.2 months. The median duration of survival was 4 months for the 80 patients who exhibited congestive heart failure on presentation. (From Kyle and Gertz [5]; with permission.)

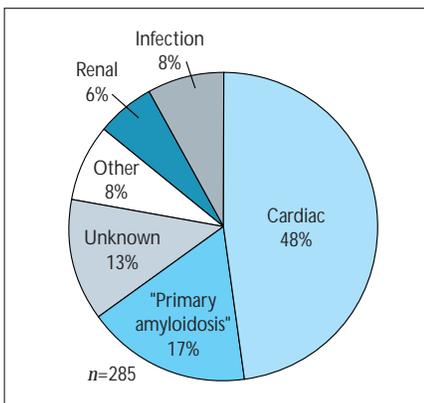


FIGURE 3-39

Causes of death in patients with primary systemic amyloidosis in an 11-year study at the Mayo Clinic. Of the 285 patients who died, death was attributed to cardiac involvement from congestive heart failure or arrhythmias in 48%. The actual percentage of cardiac-related deaths was probably higher because some patients whose death was attributed to primary amyloidosis almost certainly had terminal cardiac arrhythmia. (Adapted from Kyle and Gertz [5]; with permission.)

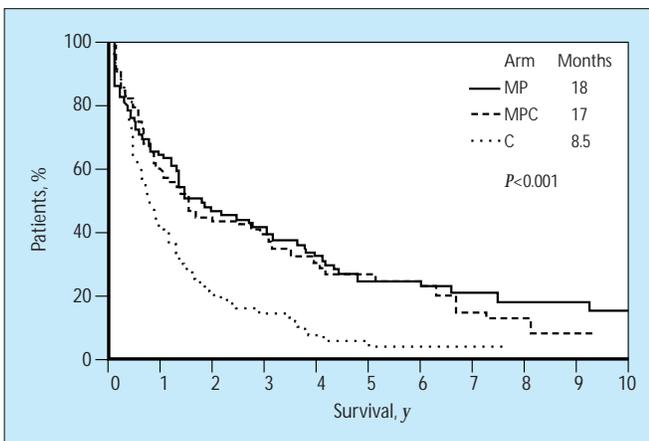


FIGURE 3-40

Survival curves in patients with primary systemic amyloidosis. Because amyloid fibrils consist of monoclonal immunoglobulin light chains, treatment with alkylating agents that are effective against plasma cell neoplasms is warranted. We treated 220 patients who had positive results on biopsy. The patients were randomized to receive colchicine (C, 72 patients), melphalan and prednisone (MP, 77), or melphalan, prednisone, and colchicine (MPC, 71). Patients were stratified according to their chief clinical manifestations: renal disease (105 patients), cardiac involvement (46), peripheral neuropathy (19), or other (50). The median duration of survival after randomization was 8.5 months in the colchicine group; 18 months in the group assigned to melphalan and prednisone; and 17 months in the group assigned to melphalan, prednisone, and colchicine ($P < 0.001$). In patients who had a reduction in serum or urine monoclonal protein at 12 months, the overall duration of survival was 50 months; whereas among those without a reduction in monoclonal protein at 12 months, the duration of survival was 36 months ($P < 0.003$). Thirty-four patients (15%) survived for 5 years or longer. (Adapted from Kyle *et al.* [12]; with permission.)

OTHER THERAPY FOR PRIMARY AMYLOIDOSIS

High-dose dexamethasone
Stem cell transplantation
4'-iodo-4'-deoxydoxorubicin

FIGURE 3-41

Other therapy for primary amyloidosis. High-dose dexamethasone has been reported to be beneficial in treating patients with primary systemic amyloidosis [13]. More intensive therapy consisting of high-dose chemotherapy followed by rescue with peripheral stem cells shows promise [14]. The introduction of 4'-iodo-4'-deoxydoxorubicin, which has an affinity for amyloid fibrils, may be an important treatment option [15].

Secondary Amyloidosis

CAUSES OF SECONDARY AMYLOIDOSIS

Cause	Patients, n
Rheumatic disease	
Rheumatoid arthritis	31
Ankylosing spondylitis	5
Other	6
Total	42
Infection	
Inflammatory bowel disease	6
Bronchiectasis	5
Osteomyelitis	5
Other	3
Total	19
Malignancy	2
None	1

FIGURE 3-42

Causes of secondary amyloidosis. Rheumatoid arthritis is the most frequent cause of secondary amyloidosis. In our study of 64 patients, rheumatoid arthritis was present for a median of 18 years before the diagnosis was made [16]. Inflammatory bowel disease, bronchiectasis, and osteomyelitis are not uncommon causes of secondary amyloidosis. (From Gertz and Kyle [16]; with permission.)

PRESENTING CLINICAL FEATURES OF SECONDARY AMYLOIDOSIS

Feature	Patients, %
Proteinuria or renal insufficiency	91
Diarrhea, obstipation, or malabsorption	22
Goiter	9
Hepatomegaly	5
Neuropathy or carpal tunnel syndrome	3
Lymphadenopathy	2
Hematuria	2
Cardiac amyloidosis	0

FIGURE 3-43

Presenting features of secondary amyloidosis. Proteinuria is the most frequent laboratory finding in patients with secondary amyloidosis. Involvement of the gastrointestinal tract as manifested by diarrhea, obstipation, or malabsorption occurred in one fifth of our patients. Treatment of secondary amyloidosis depends on the underlying disease. Familial Mediterranean fever frequently is associated with secondary amyloidosis unless the patient is treated with colchicine. (From Gertz and Kyle [16]; with permission.)

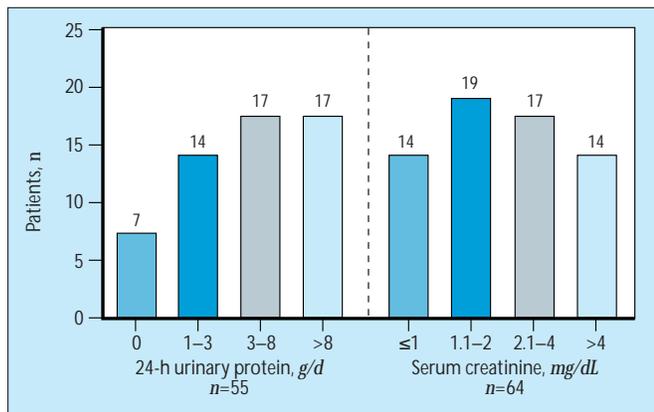


FIGURE 3-44

Proteinuria and renal insufficiency in patients with secondary amyloidosis. The clinical target organ was the kidney in 91% of patients. (From Gertz and Kyle [16]; with permission.)

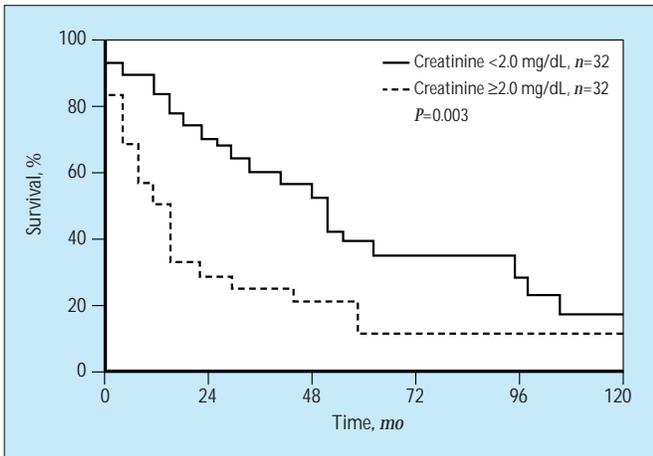


FIGURE 3-45

Association between serum creatinine levels and survival in patients with secondary amyloidosis. A serum creatinine value of 2 mg/dL or more was associated with a shorter survival than was a value of less than 2 mg/dL. (From Gertz and Kyle [16]; with permission.)

Familial Amyloidosis

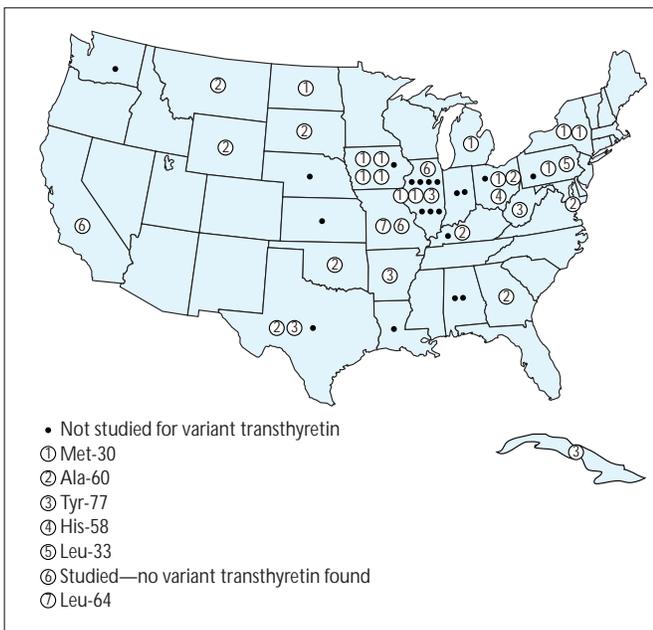


FIGURE 3-46

Wide geographic distribution of familial amyloidosis. Familial or hereditary amyloidosis has an autosomal dominant pattern of inheritance. It accounts for 3.5% of our cases of amyloidosis. In our practice, the geographic distribution is wide and not associated with clustering. Frequently, a family history of amyloidosis was not obtained until after amyloidosis was diagnosed [17]. More than 50 transthyretin mutations have been recognized [18]. (Adapted from Gertz et al. [17]; with permission.)

CLASSIFICATION OF FAMILIAL AMYLOIDOSIS

Classification	Major protein component
Neuropathic: Portugal, Japan, Sweden, and other countries	Transthyretin (prealbumin)
Cardiopathic: Denmark and Appalachia in the United States	Transthyretin (prealbumin)
Nephropathic: familial Mediterranean fever	Protein A

FIGURE 3-47

Classification of familial amyloidosis. Clinically, familial amyloidosis can be classified most easily as neuropathic, cardiopathic, or nephropathic. The neuropathic form is characterized by a sensorimotor peripheral neuropathy beginning in the lower extremities. Disturbances

of bladder and gastrointestinal function are common. Late onset may occur with the development of symptoms in the seventh or eighth decade of life. The nephropathic form is most often caused by familial Mediterranean fever. This form affects persons of Mediterranean descent and is characterized by recurrent episodes of fever and abdominal pain that begin in childhood.

Familial amyloidosis involving the kidneys has been reported by Ostertag [19] and others [20–22]. Families with apolipoprotein A1 mutation, as well as mutations in the fibrinogen α -chain gene, have been recognized. On presentation, patients with renal involvement exhibit hypertension and mild renal insufficiency that progresses to end-stage renal failure. The amyloid deposits have mutations in the fibrinogen α -chain gene. This form of amyloidosis is autosomal dominant. No peripheral neuropathy develops, and the onset of renal disease occurs in the fifth to seventh decades of life. The mutation consists of the substitution of glutamic acid for valine at position 526 of the fibrinogen chain. A mutation in fibrinogen has been described at position 554 [23,24]. A rare form of inherited secondary amyloidosis produces nephropathy, deafness, and urticaria. This form has been referred to as the Muckle-Wells syndrome [25]. (*Adapted from Kyle and Gertz [26].*)

Dialysis-Associated Amyloidosis



FIGURE 3-48

Radiograph showing carpal tunnel syndrome in a patient with dialysis-associated amyloidosis. Long-term hemodialysis often results in carpal tunnel syndrome with pain involving the shoulders, hands, wrists, hips, and knees. Cystic radiolucencies are common in the carpal bones. Pathologic fractures have occurred from large amyloid deposits. The major component of the amyloid is β_2 -microglobulin. (*From Gertz and Kyle [3]; with permission.*)

RATE OF AMYLOIDOSIS (β_2 -MICROGLOBULIN) WITH DIALYSIS

Years of dialysis	Patients with amyloidosis, %
10	20
15	30–50
>20	80–100

FIGURE 3-49

Amyloidosis (β_2 -microglobulin) with dialysis. The duration of dialysis is directly associated with the incidence of amyloidosis. Dialysis-associated amyloidosis will develop in more than 80% of patients after 20 years of dialysis. It occurs with both hemodialysis and peritoneal dialysis. The amyloid deposition is systemic; however, involvement of visceral organs is usually modest [27,28]. Renal transplantation often leads to dramatic improvement in joint symptoms. A β_2 -microglobulin-adsorbent column may be useful in therapy [29].

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