

# Amyloidosis, Primary Systemic

# Background

- Systemic amyloidosis can be classified as follows:
- (1) primary systemic amyloidosis (PSA), usually with no evidence of preceding or coexisting disease, paraproteinemia, or plasma-cell dyscrasia;
- (2) amyloidosis associated with multiple myeloma; or
- (3) secondary systemic amyloidosis with evidence of coexisting previous chronic inflammatory or infectious conditions.

# Background

- Primary systemic amyloidosis involves mainly mesenchymal elements, and cutaneous findings are observed in 30-40% of patients.
- Secondary systemic amyloidosis does not involve the skin, whereas localized amyloidosis does.

- Primary systemic amyloidosis involves the deposition of insoluble monoclonal immunoglobulin (Ig) light (L) chains or L-chain fragments in various tissues, including smooth and striated muscles, connective tissues, blood vessel walls, and peripheral nerves.
- The amyloid of primary systemic amyloidosis is made by plasma cells in the bone marrow. These L-chains are secreted into the serum. Unlike the normal L-chain and the usual form seen in patients with myeloma, these L-chains are unique in that they undergo partial lysosomal proteolysis within macrophages, and they are extracellularly deposited as insoluble amyloid filaments attached to a polysaccharide.
- Sometimes, instead of an intact L-chain, this amyloid has the amino-terminal fragment of an L-chain.

# Causes

- Primary systemic amyloidosis is a plasma-cell dyscrasia characterized by an autonomous proliferation of plasma cells with an overproduction of a monoclonal Ig protein

# Pathophysiology

- The final pathway in the development of amyloidosis is the production of amyloid fibrils in the extracellular matrix.
- The process by which precursor proteins produce fibrils appears to be multifactorial and differs among the various types of amyloidosis.

# Pathophysiology

- The fibrils in primary systemic amyloidosis are composed of Ig L-chain material (protein amyloid L) consisting of intact L-chains, L-chain fragments (particularly the variable amino-terminal region), or both. Amyloid deposition occurs as a result of plasma-cell dyscrasia.

# Pathophysiology

- The diagnosis depends on the demonstration of amyloid deposits in tissue.
- The organs most commonly involved are the kidneys or heart, either individually or together.
- Autonomic and sensory neuropathies are relatively common features.



About 30-40% of patients with primary systemic amyloidosis have cutaneous findings.

- *Mucocutaneous involvement provides early evidence of the existence of an underlying plasma-cell dyscrasia.*
- *Petechiae, purpura, and ecchymoses that occur spontaneously or after minor trauma are the most common skin signs and are found in about 15-20% of patients.*

The most characteristic skin lesions consist of papules, nodules, and plaques that are waxy, smooth, and shiny.

- *Scalp involvement may be evident with hair loss.*
- *Mucocutaneous changes in the oral cavity include localized rubbery papules, petechiae, and ecchymoses.*
- *Xerostomia may result from the infiltration of the salivary glands.*
- *Macroglossia is reported in 19% of patients with primary systemic amyloidosis.*

- Primary systemic amyloidosis accounts for 7% of nonhematological malignancies, but few cases of gastric carcinoma in patients with primary amyloidosis have been described.
- *Although acute pseudoobstruction is an uncommon clinical manifestation of amyloidosis, the coexistence of both gastrointestinal hemorrhage and pseudoobstruction of the small intestine should alert the clinician to a diagnosis of gastrointestinal amyloidosis.*

# Race

- No racial predilection is reported for the development of primary systemic amyloidosis.

# Sex

- No sexual predilection is reported for primary systemic amyloidosis; however, Kyle and Greipp reported a slight male dominance in a large series of 182 patients with primary systemic amyloidosis

# Age

- Primary systemic amyloidosis is a disease of adulthood. In reported cases, the mean patient age of onset is 65 years.

# History

- The symptoms of a patient with primary systemic amyloidosis (PSA) are rarely helpful in making the diagnosis because they are often too nonspecific. Therefore, the diagnosis is often delayed.

# Presenting symptoms include the following:

- Fatigue
- Weight loss
- Paresthesias
- Hoarseness
- Edema
- Classically, patients present with symptoms of the following:
- Carpal tunnel syndrome
- Macroglossia
- Mucocutaneous lesions
- Hepatomegaly
- Edema



- The organs most commonly involved are the kidneys or heart, either individually or together.
- The patients' symptoms reflect the organ or organs most prominently involved.

# Physical

- Clinically evident mucocutaneous involvement occurs in 30-40% of patients with primary systemic amyloidosis, and it provides an early clue to the existence of an underlying plasma-cell dyscrasia.

Petechiae and ecchymoses are the most common skin findings, because of cutaneous blood vessel involvement.

- The face is most commonly affected; minor trauma sometimes precipitates eyelid and periorbital purpura (pinch purpura or raccoon eyes sign).
- Purpuric lesions are found in flexural regions such as the nasolabial folds, neck, and axillae.
- At times, bullae form; these may be hemorrhagic.

- The most characteristic skin lesion in primary systemic amyloidosis consists of waxy papules, nodules, or plaques that may be evident in the eyelids, retroauricular region, neck, or inguinal and anogenital regions.
- Plaques may coalesce to form large tumefactive lesions.
- Diffuse infiltrates may resemble infiltrates of scleroderma or myxedema.

- Scalp involvement may appear as diffuse or patchy alopecia.
- Dystrophic nail changes include brittleness, crumbling, and subungual striation.
- The tongue may be infiltrated, resulting in macroglossia. Macroglossia is a classic feature of primary systemic amyloidosis. The tongue may extrude through gaps between the teeth to produce unique irregular indentations.
- The presence of amyloid in the oral cavity is often revealed by localized, soft, elastic papules

- Amyloid deposition in the smooth and striated muscles, connective tissue, blood vessel walls, and peripheral nerves may result in myocardial insufficiency, which is the most common cause of death in this fatal disease.

- Cardiac infiltration may cause angina, infarction, arrhythmias, or orthostatic hypotension.
- Blood vessel infiltration may lead to claudication of the legs or jaw.



- Renal amyloidosis usually manifests as proteinuria, often resulting in nephrotic syndrome.
- Edema is frequently found and may be the result of cardiac failure or nephrotic syndrome.

- Amyloid infiltration of the gastrointestinal tract may result in hemorrhage or malabsorption. Gut bleeding may also be fatal.
- Hepatomegaly occurs in about 50% of patients with primary systemic amyloidosis, but splenomegaly is present in less than 10% of patients.

- Autonomic and sensory neuropathies are relatively common features.
- Autonomic neuropathy may result in symptomatic postural hypotension, impotence, and disturbances in gastrointestinal motility.

# Laboratory Studies

- Laboratory studies revealed anemia in less than 50% of the cases. The white cell count was usually within the reference range, and the erythrocyte sedimentation rate was higher than 50 mm/h in one half of the cases. Hepatic function was abnormal, and the serum creatinine level was increased in 50% of patients. Proteinuria was present in more than 90% of the cases.
- Conventional urine heat testing and electrophoresis of serum and urine samples may fail to demonstrate small quantities of monoclonal paraprotein or Bence-Jones protein. Immunoelectrophoresis of serum and concentrated urine samples is essential.

# Imaging Studies

- Echocardiography is valuable in the evaluation of amyloid heart disease. It usually reveals a concentrically thickened left ventricle and often a thickened right ventricle, with a normal-to-small cavity.
- Doppler studies are useful and may show abnormal relaxation early in the course of the disease. Advanced involvement is characterized by restrictive hemodynamics.

# Procedures

- Biopsy of a cutaneous lesion, if present, has the advantage of safety and a high diagnostic yield.
- Biopsy results in clinically normal skin may be positive in as many as 50% of cases of primary systemic amyloidosis.
- Findings from abdominal fat aspiration are positive in almost 80% of patients.
- Rectal biopsy reveals positive findings in about 80% of patients.
- If specimens from the biopsy sites are negative for amyloid, tissue should be obtained from an organ or area with suspected involvement, such as the kidney, liver, heart, or sural nerve.

# Histologic Findings

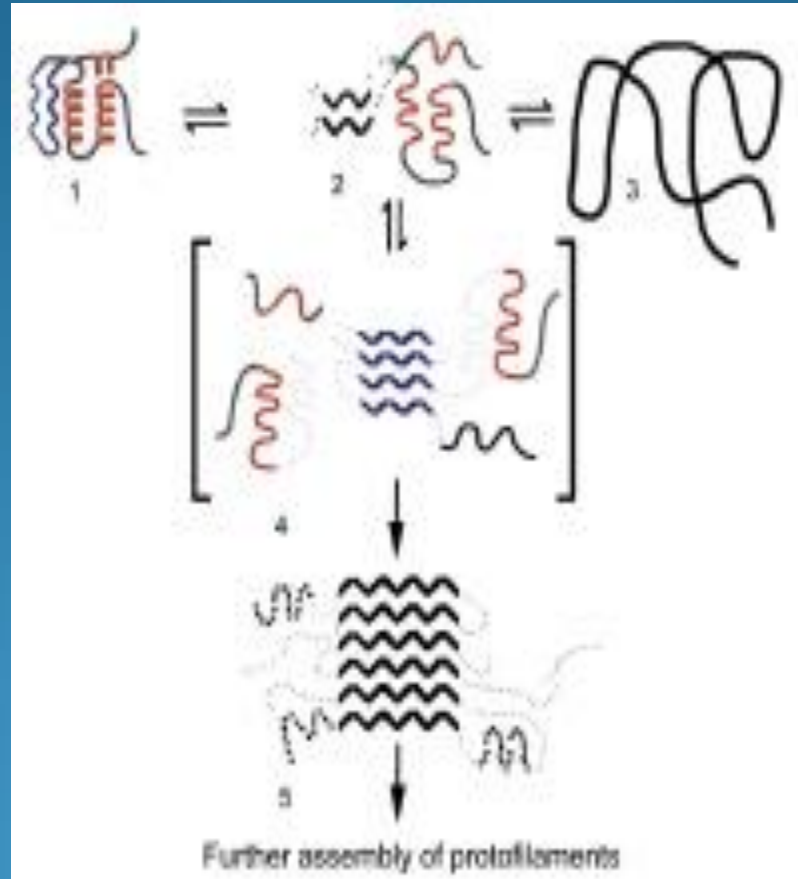
- The best way to identify amyloid is to stain paraffin-embedded sections with alkaline Congo red and to examine them with polarized light to elicit a green fluorescence. Routine hematoxylin-eosin staining may show a homogenous, faintly eosinophilic mass if enough amyloid is present.
- Analysis of a skin biopsy specimen of a papule reveals an amorphous or fissured eosinophilic mass in the papillary dermis with associated thinning or obliteration of the rete ridges. Nodules and plaques may demonstrate diffuse amyloid deposition in the reticular dermis or subcutis. Amyloid depositions are usually not associated with an inflammatory infiltrate.
- The appearance of amyloid infiltration of the blood vessel walls, pilosebaceous units, arrector pili muscles, and lamina propria of sweat glands and infiltration around individual fat cells in the subcutis (known as amyloid rings) are characteristic findings. Amyloid may be deposited in the nail bed of dystrophic nails.

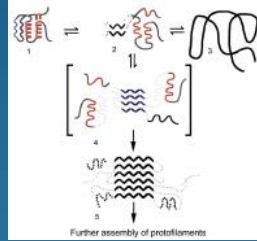
# Amyloidosis, Familial Renal

- Amyloidosis is a disorder of protein folding in which normally soluble proteins undergo a conformational change and are deposited in the extracellular space in an abnormal fibrillar form, as shown below.
- Accumulation of these fibrils causes progressive disruption of the structure and function of tissues and organs, and the systemic (generalized) forms of amyloidosis are frequently fatal.
- The conditions that underlie amyloid deposition may be either acquired or hereditary, and at least 20 different proteins can form amyloid fibrils in vivo



# Proposed mechanism for amyloid fibril formation.





- The drawing depicts a generic amyloid fibril precursor protein (I) in equilibrium with a partially unfolded, molten, globulelike form of the protein (II) and its completely denatured state (III).
- Autoaggregation through the beta domains initiates fibril formation (IV), providing a template for ongoing deposition of precursor proteins and for the development of the stable, mainly beta-sheet, core structure of the fibril.
- The amyloidogenic precursor proteins in patients with familial renal amyloidosis are thought to be less stable than their wild-type counterparts, causing them to populate intermediate, molten, globulelike states more readily.

- Renal dysfunction is one of the most common presenting features of patients with systemic amyloidosis, and amyloid accumulation is the major pathological finding in approximately 2.5% of all native renal biopsies.
- Most such patients have either reactive systemic (AA) amyloidosis or monoclonal immunoglobulin light-chain (AL) amyloidosis, but in the few remaining cases, the disease is hereditary.

- The syndrome of familial systemic amyloidosis with predominant nephropathy is inherited in an autosomal dominant manner and was first described in a German family by Ostertag in 1932.
- Research has shown that almost all patients with familial renal amyloidoses (FRA) are heterozygous for mutations in the genes for lysozyme, apolipoprotein AI, apolipoprotein AII, or fibrinogen A alpha-chain and that the amyloid fibrils in this condition are derived from the respective variant proteins.
- Both penetrance and the clinical phenotype can vary substantially among different families with the same mutation, even within individual kindreds.

# Causes

- Susceptibility to FRA is inherited in an autosomal dominant manner. In nearly all cases, the disease results from mutations in the genes encoding the 4 plasma proteins, lysozyme, apolipoprotein AI, apolipoprotein AII, and fibrinogen A alpha-chain.
- In a small number of families, the cause has not yet been determined.

# Pathophysiology

- The pathogenesis of amyloid centers around off-pathway folding of the various amyloid fibril precursor proteins.
- These proteins can exist as 2 radically different stable structures, the normal soluble form and a highly abnormal fibrillar conformation.

# Pathophysiology

- All amyloid fibrils share a common core structure in which the subunit proteins are arranged in a stack of twisted, antiparallel, beta-pleated sheets lying with their long axes perpendicular to the fibril long axis.
- Proteins that can form amyloid transiently populate partly unfolded intermediate molecular states that expose the beta-sheet domain, enabling them to interact with similar molecules in a highly ordered fashion.
- Propagation of the resulting low molecular weight aggregates into mature amyloid fibrils is probably a self-perpetuating process that depends only on a sustained supply of the fibril precursor protein.
- In some cases, the precursors undergo partial proteolytic cleavage; however, whether this occurs before, during, or after the formation of amyloid fibrils remains unknown.

# Pathophysiology

Amyloid deposits in all different forms of the disease, both in humans and in non-human animals, contain the nonfibrillar glycoprotein amyloid P component (AP).

- AP is identical to and derived from the normal circulating plasma protein, serum amyloid P component (SAP), a member of the pentraxin protein family that includes C-reactive protein.
- SAP consists of 5 identical subunits, each with a molecular mass of 25.462 kD, which are noncovalently associated in a pentameric disklike ring.
- The SAP molecule is highly resistant to proteolysis, and, although not itself a proteinase inhibitor, its reversible binding to amyloid fibrils in vitro protects them against proteolysis.
- In contrast to its normal rapid clearance from the plasma, SAP persists for very prolonged periods within amyloid deposits.
- The possibility that SAP may contribute to the pathogenesis and/or persistence of amyloid deposits in vivo has been confirmed in studies on SAP knockout mice.



# Pathophysiology

- Amyloid deposits accumulate in the extracellular space, progressively disrupting the normal tissue architecture and consequently impairing organ function.
- Amyloid deposits can also produce space-occupying effects at both microscopic and macroscopic levels.
- Although amyloid is inert in the sense that it does not stimulate either a local or systemic inflammatory response, some evidence suggests that the deposits exert cytotoxic effects and possibly promote apoptosis.
- Strong clinical impressions exist that suggest the rate of accumulation of amyloid has a major bearing on organ function, which can be preserved for very long periods in the presence of an extensive but stable amyloid load.
- This may reflect adaptation to gradual amyloid accumulation or may relate to toxic properties of newly formed amyloid material.

# Pathophysiology

- Prospective studies with serial SAP scintigraphy, a specific and semiquantitative nuclear medicine technique for imaging amyloid deposits, have confirmed that amyloid deposits are turned over constantly, albeit at a relatively low and variable rate.
- Therefore, the course of a particular patient's amyloid disease depends on the relative rates of amyloid deposition versus turnover.
- Amyloid deposits often regress when the supply of the respective fibril precursor protein is reduced, and, under favorable circumstances, this is accompanied by stabilization or recovery of organ function.

# Pathophysiology

- Many questions about amyloid deposition remain unanswered.
- Why only a small number of unrelated proteins form amyloid in vivo remains unclear, and, as yet, little is known about the genetic or environmental factors that determine individual susceptibility to amyloid or factors that govern its anatomical distribution and clinical effects.
- Hereditary amyloid deposition starts in the first or second decade in some patients, but possibly not until much later in life in other patients.
- In addition, the mechanism by which amyloid deposits are cleared and why the rate of this varies so substantially among patients are not understood.

# Mortality/Morbidity

- The natural history of familial renal amyloidosis is a relentless gradual progression, leading to renal and sometimes other organ failure and, eventually, death.
- Amyloid deposits can ultimately affect many organ systems, but they may be widespread and very extensive without causing symptoms.
- The rate of progression and course of disease are extremely variable, and some patients with clinically overt involvement of multiple organs survive for many years or decades.
- Overall, the prognosis of patients with FRA is much better than that of those with acquired AA and AL amyloidosis.

# Race

- Most patients are of northern European Caucasian ancestry, but fibrinogen A alpha-chain amyloidosis has been reported in Peruvian-Mexican, Korean, and African American families, and the authors are presently investigating a northern Indian family with uncharacterized FRA.

# Sex

- Gene carriage and the incidence of clinical disease are equal between men and women.

# Age

- FRA may manifest any time from the first decade to old age but most typically in mid adult life. The age at presentation, like other clinical features, varies among mutations and even within individual kindreds.

# History

- Patients typically present with proteinuria and/or hypertension followed by progressive renal failure.
- The latter may evolve extremely slowly, and patients with hereditary apolipoprotein AI and lysozyme amyloidosis may not develop end-stage renal failure for several decades.
- In contrast to AL amyloidosis, orthostatic hypotension is unusual, probably because autonomic involvement and amyloid cardiomyopathy are rare in FRA.



# History

- Many patients give a clear autosomal dominant family history of renal disease, but penetrance is variable.

# History

- Patients with FRA who do not give a family history are readily misdiagnosed as having acquired AL amyloidosis.
- Patients with variant lysozyme amyloidosis usually have substantial GI amyloid deposits that may result in poor gastric emptying, but these patients often remain asymptomatic until an acute crisis occurs.
- The upper GI tract is perforated easily and has a tendency to bleed profusely should gastric erosions or peptic ulceration occur.

# History

- At presentation, most patients with this type of FRA have substantial amounts of amyloid in the kidneys, spleen, and liver, but the course of the disease tends to be remarkably slow.
- Even in the presence of massive hepatosplenomegaly, liver failure rarely occurs; however, spontaneous hepatic rupture has been reported in several cases.

# History

- Cardiac amyloid and neuropathy are not features of lysozyme amyloidosis, but petechial rashes starting in childhood are associated with the lysozyme Ile56Thr variant.
- The features of hereditary apolipoprotein AI amyloidosis vary significantly with different mutations.
- Patients with the most common amyloidogenic Gly26Arg variant usually present with hypertension and proteinuria and develop progressive renal impairment.
- Many mutations are associated with extensive but clinically silent amyloid deposits in the liver and spleen.

# History

- Amyloid cardiomyopathy, gut involvement, and skin and laryngeal deposits occur occasionally, and a few patients with variant apolipoprotein AI Glu26Arg and Leu178His develop a progressive neuropathy resembling familial amyloid polyneuropathy, a disease that is usually associated with transthyretin mutations.

# History

- Hereditary apolipoprotein AII amyloidosis appears to predominantly cause renal disease.
- Progression to end-stage renal failure occurs, and at least 2 patients have renal grafts that have functioned for more than a decade.
- There is one report of a patient with long-standing renal failure who subsequently developed evidence of amyloid cardiomyopathy.
- Most patients diagnosed with fibrinogen A alpha-chain Glu526Val amyloidosis present in late-middle age with proteinuria or hypertension and progress to end-stage renal failure during the following 5-10 years.
- Amyloid deposition occurs predominantly in the kidneys and also variably in the spleen, liver, and adrenal glands

# History

- Clinically significant neuropathy or cardiac amyloid deposition does not seem to occur in patients with the Glu526Val variant, and liver failure is very rare.
- The other 3 mutations that cause fibrinogen A alpha-chain amyloidosis have been identified in too few families to make generalizations, other than that these mutations are predominantly associated with renal disease.

# Physical

- Clinical features and their association with particular mutations are shown in the Table.
- Hypertension and edema occur in most patients diagnosed with FRA.
- Hepatosplenomegaly is quite common and is probably most common in patients with the apolipoprotein AI type.
- Congestive cardiac failure resulting from restrictive amyloid cardiomyopathy occurs in some patients with variant apolipoprotein AI Leu60Arg and is the predominant feature in patients with the variants Arg173Pro and Leu174Ser.
- A symmetrical sensorimotor polyneuropathy occurs in some patients with the apolipoprotein AI Gly26Arg and Leu178His variants.
- Laryngeal and cutaneous deposits producing hoarseness, infiltrative plaques, and petechial rashes are associated with the apolipoprotein AI Arg173Pro, Ala175Pro, Leu90Pro, and Leu178His variants, and petechial rashes also occur in patients with lysozyme Ile56Thr.



# Laboratory Studies

- No blood or urine test result is diagnostic of amyloidosis, but lab findings that exclude chronic inflammation or a monoclonal gammopathy in a patient with renal amyloid accumulation support the possibility of FRA. Lab tests also have a vital role in evaluating and monitoring amyloidotic organ function.
- Once the creatinine clearance has fallen to less than 20%, progression to end-stage renal failure is almost inevitable, although the rate of decline often does not accord with predictions and may be remarkably slow. On the other hand, step-wise deteriorations in renal function occur quite frequently, even in the absence of any identifiable intercurrent renal insult such as dehydration, infection, or venous thrombosis.
- Liver function test results tend to remain normal until the liver has been extensively infiltrated by amyloid, and even marked hepatomegaly may be accompanied by only a modest elevation in serum alkaline phosphatase. Liver function in those with FRA is often well preserved for decades, and elevations of serum bilirubin and transaminase levels occur at a very late stage. A bilirubin value of just twice the upper limit of normal is associated with a very poor prognosis and incipient liver failure.
- Hematological indices and coagulation tend to be unremarkable, although a hyposplenic picture can occur. Occult GI blood loss should be considered in patients with anemia that is not secondary to renal impairment.

# Imaging Studies

- Anatomical imaging modalities (eg, plain radiography, computed tomography [CT] scan, magnetic resonance imaging [MRI], ultrasonography)
- Typically, these yield nonspecific findings in patients with systemic amyloidosis

# Imaging Studies

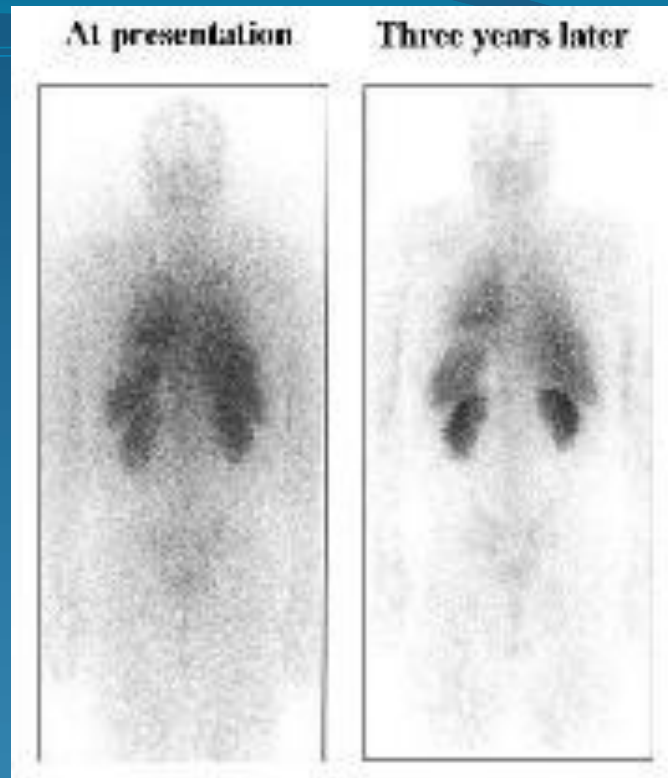
- Heart - Myocardial thickness, pericardial and pleural effusion, and typical echogenic subendocardial depositions
- Liver and spleen - Spontaneous subcapsular hemorrhages
- Intestine - Inhomogeneous, patchy-like depositions
- Kidney - Somewhat unspecific results in this organ

# Imaging Studies

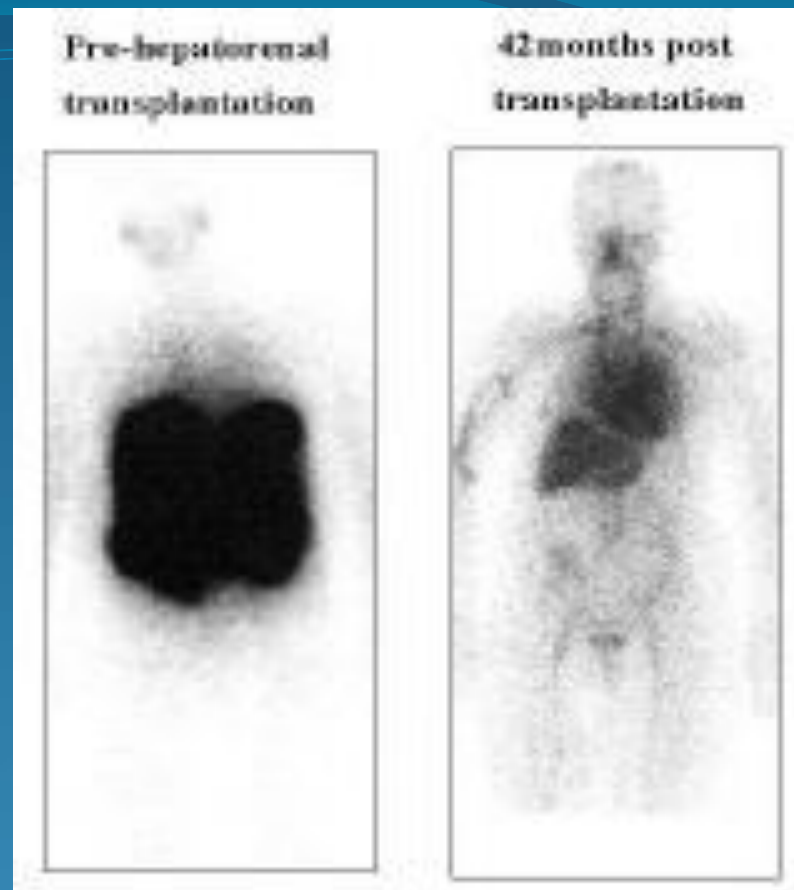
- Amyloidotic organs may be enlarged in the late stage of the disease, but kidney size varies and may be normal or even small at presentation.
- Amyloid deposits are rich in calcium, and areas of calcification may develop.

Radionuclide tracers used for bone scintigraphy occasionally localize in amyloidotic organs.

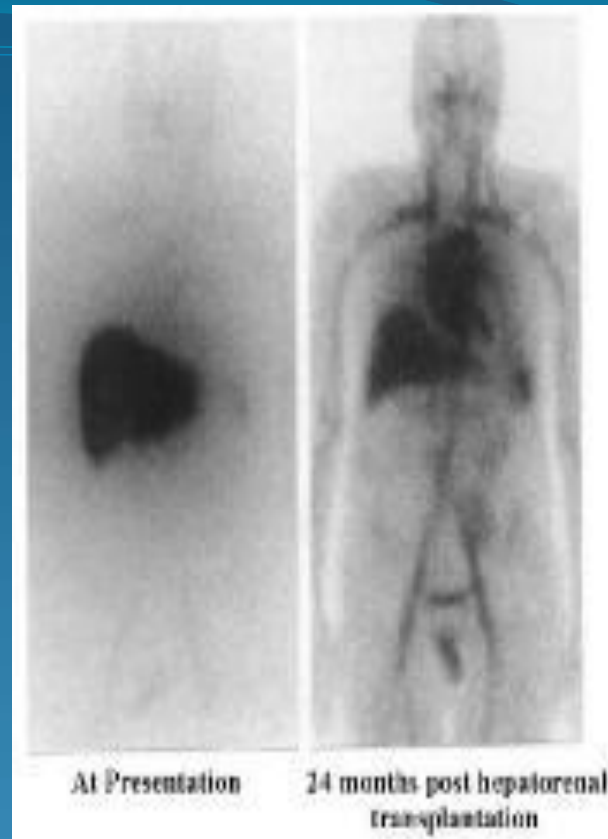
SAP component scintigraphy



- Progression of amyloid deposits in a patient with amyloidosis associated with fibrinogen A alpha-chain Glu526Val. These serial posterior, whole-body, scintigraphic images were obtained following intravenous injection of iodine-123 ( $^{123}\text{I}$ )-labeled human serum amyloid P component into a 48-year-old man with hereditary amyloidosis associated with fibrinogen A alpha-chain Glu526Val in whom asymptomatic proteinuria had been identified. Both parents were alive and well and older than age 80 years. The scan at diagnosis (left) showed modest abnormal uptake into renal amyloid deposits, which increased at follow-up 3 years later (right).



- Regression of amyloidosis associated with fibrinogen A alpha-chain Glu526Val following hepatorenal transplantation. The pictures are serial anterior, whole-body, scintigraphic images obtained following intravenous injection of iodine-123 (<sup>123</sup>I)-labeled human serum amyloid P component into a patient with amyloidosis associated with fibrinogen A alpha-chain Glu526Val. Prior to hepatorenal transplantation (left), heavy amyloid deposition was present in an enlarged liver and spleen. No amyloid deposits were identified in a follow-up study obtained 42 months after hepatorenal transplantation (right); only a normal distribution of tracer is present throughout the blood pool.



- Regression of amyloidosis associated with apolipoprotein AI Gly26Arg following hepatorenal transplantation. These serial anterior, whole-body, scintigraphic images were obtained following intravenous injection of iodine-123 ( $^{123}\text{I}$ )-labeled human serum amyloid P component into a patient with hereditary amyloidosis associated with apolipoprotein AI Gly26Arg. Prior to hepatorenal transplantation (left), heavy amyloid deposition was present in the liver, obscuring the kidneys. Two years after combined hepatorenal transplantation (right), a follow-up scan was normal, showing tracer distributed evenly throughout the background blood pool, including the transplanted organs. Splenic amyloid deposits that were evident initially in posterior scans had regressed at follow-up.



# Echocardiography

- Significant cardiac amyloid deposition is relatively unusual in patients with FRA, especially in patients with lysozyme and fibrinogen types, but confers a poor prognosis when it is present.
- Amyloid causes diastolic dysfunction with well-preserved contractility until a very late stage.
- Cardiac amyloidosis is best evaluated by a combination of echocardiography, ECG, and measurement of NT-pro BNP.
- The classic findings with 2-dimensional Doppler echocardiography are concentric biventricular wall thickening, increased myocardial echodensity, thickened but pliable valves, and a restrictive filling pattern.
- ECG findings may be normal in patients with substantial cardiac amyloidosis, but reduced voltages, pathological Q waves (ie, pseudoinfarct pattern) in the anterior chest leads, and conduction abnormalities usually signify advanced disease.

# DNA analysis

- DNA analysis is mandatory in all patients with systemic amyloidosis who cannot be confirmed absolutely to have the AA or AL type. Appreciating that the presence of a chronic inflammatory disease or a monoclonal gammopathy may be incidental is important.
- Numerous mutations have been identified in most of the genes associated with hereditary amyloidosis, and new variants are being found regularly. Therefore, performing gene sequencing is better than using methods such as restriction fragment length polymorphism analysis, which is directed at particular known mutations.
- The results of DNA analysis are not, by themselves, definitive proof of the presence of amyloid or the amyloid fibril type, and these findings must be interpreted in light of other clinical and histologic findings.

# Fibril protein sequencing

- In cases in which identifying the amyloid fibril type by more conventional means is not possible, isolation of amyloid fibrils from a sample of fresh amyloidotic tissue enables amino acid sequencing of the fibril subunit peptide.
- This requires technical expertise and is time consuming but can be achieved using very small tissue samples. It is the most definitive method for typing amyloid deposits.

# Procedures

- The definitive diagnosis of amyloid accumulation requires histologic confirmation; however, biopsy procedures carry an increased risk of hemorrhage in patients with amyloidosis, and bleeding may be substantial and even life-threatening in 5% of patients who undergo biopsies. This is due to the increased fragility of amyloidotic blood vessels and the reduced elasticity of severely affected organs.
- Less-invasive alternatives include fine-needle aspiration of subcutaneous fat and rectal or labial salivary gland biopsy. In experienced hands, these screening biopsies can yield positive results in as many as 80% of cases; however, in routine practice, sensitivity is only approximately 50%. Also, fat aspirates are usually not suitable for immunohistochemical typing.

# Histologic Findings

- The appearance of amyloid fibrils in tissues under the electron microscope is not always completely specific, and, sometimes, they cannot be identified convincingly. Although electron microscopy should be more sensitive than light microscopy, it is not sufficient by itself to confirm the diagnosis of amyloidosis.

# Amyloidosis, Beta2M (Dialysis-Related)

# Background

- Beta-2-microglobulin amyloidosis is a disabling condition that affects patients undergoing long-term hemodialysis (HD) or continuous ambulatory peritoneal dialysis (CAPD).[1, 2] Case reports involving patients with near end-stage renal disease also exist. It does not affect individuals with normal or mildly reduced renal function or patients with a functioning renal transplant.
- Beta-2-microglobulin is a major constituent of amyloid fibrils.[3] Its accumulation has been shown to invade synovial membranes and osteoarticular sites, causing destructive osteoarthropathies, such as carpal tunnel syndrome, flexor tenosynovitis, subchondral bone cysts, and erosions, as well as pathologic fractures.
- Visceral involvement has been found in different organs, such as the gastrointestinal tract, heart, and tongue, but overt manifestations are rare.