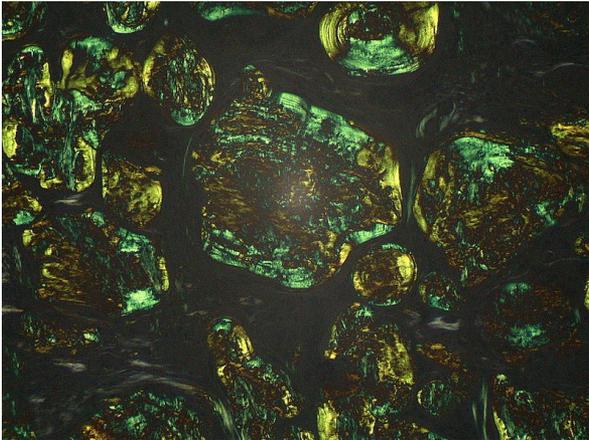


A Guide To AL (Light Chain) Amyloidosis

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What is amyloidosis?

Amyloidosis is a disorder in which misfolded native proteins deposit extracellularly and lead to organ damage. Although the various types of amyloidoses share in common the deposition of misfolded proteins that aggregate as fibrils in tissue, they differ in actual protein composition, organ involvement, prognostic implication and most importantly, treatment. It is therefore *critically* important to determine the type of amyloidosis a patient has in order to provide the appropriate treatment.

There are at least 23 different proteins associated with amyloidosis. The most common type of amyloidosis and the one that is associated with a poor prognosis if left untreated is called **AL amyloidosis and due to the deposition of clonal immunoglobulin light chains** produced by plasma cells in the bone marrow.

There are several types of hereditary amyloidoses, most common of which is **mATTR amyloidosis**, an autosomal dominant disease that results from misfolding of mutant transthyretin, a protein produced in the liver containing a single point gene mutation. More than 100 different transthyretin mutations are known to cause amyloidosis. The wild-type transthyretin can also misfold and aggregate as amyloid fibrils in tissues, usually the heart in the elderly Caucasian men, causing **wtTTR amyloidosis (also called senile systemic amyloidosis)**.

Other types of amyloidoses include the following. Chronic inflammatory conditions such as rheumatoid arthritis or chronic infections (such as bronchiectasis) are associated with excessive production of the inflammatory protein, serum amyloid A (SAA) that may misfold and lead to **AA amyloidosis**. Misfolding and amyloid deposition of atrial natriuretic peptide may lead to **AANP amyloidosis** located in the left atrium and increase the risk of atrial fibrillation. Other mutant proteins causing hereditary amyloidoses include apolipoproteins AI and AII, cystatin C, fibrinogen A α -chain, lysozyme, and gelsolin.

This pamphlet will concentrate on the most common type of amyloidosis, AL (light chain) amyloidosis with special emphasis on the cardiac findings. For further reference on ATTR amyloidosis, please refer to a similar pamphlet from the Amyloidosis Foundation on this topic.

What is AL (light chain) amyloidosis ?

AL amyloidosis is the disease caused by abnormal immunoglobulin light chains (LCs) produced by clonal plasma cells in the bone marrow. The abnormal LCs subsequently misfold, aggregate, and deposit in tissues as amyloid fibrils. It is part of a spectrum of clonal plasma cell proliferative disorders that include multiple myeloma, monoclonal gammopathy of undetermined significance, Waldenström's macroglobulinemia and heavy chain disease. Multiple myeloma is associated with an excessive number of bone marrow plasma cells (30% or more) producing immunoglobulin proteins, however, only about 10-15% of patients with multiple myeloma develop AL amyloidosis. Patients with AL amyloidosis usually have only a modest increase in the population of plasma cells (5-20%) in the bone marrow..

How common is AL amyloidosis?

Although AL amyloidosis is commonly thought of as a rare disease, the incidence is similar to diseases not considered rare such as Hodgkin's disease or chronic myelocytic leukemia. There are approximately 2000-2500 new cases per year in the United States. Increased awareness of the associated physical findings in amyloidosis by physicians and the better technology at the present time for recognition of LC abnormalities in blood and urine is leading to the diagnosis of AL amyloidosis at an earlier stage .

How do abnormal light chains cause pathology?

Several mechanisms probably play a role in tissue and organ injury caused by abnormal LCs. LC proteins produced by the clonal plasma cell are structurally unstable and transition through a series of intermediate conformations (monomers, dimers, oligomers) eventually attaining a non-native assembly that favors self-aggregation in tissues. Several factors have been implicated as contributing to the predisposition to form amyloid fibrils including specific amino acid substitutions, thermodynamic instability and post-translational protein modifications. The mass of amyloid deposits limits the ability of the tissue to function normally. In addition, the deposition of amyloid proteins in the extracellular space including the perivascular space in organs such as the heart, liver, gastrointestinal tract, kidneys and peripheral nerves is associated with evidence of apoptotic injury and oxidative stress. Perivascular deposition in arterioles is associated with ischemic injury in the setting of occlusive disease but is also seen even without flow limiting stenosis. Evidence from cell culture studies, animal studies and clinical changes in patients following chemotherapy suggest that circulating amyloidogenic light chains (not yet deposited as fibrils) have a toxic effect and cause direct tissue injury.

What organ systems are affected by AL amyloidosis?

AL amyloidosis is a systemic illness and can affect nearly every organ, including the heart, kidneys, lung, gastrointestinal system (liver and intestines), peripheral and autonomic nerves, and soft tissues. The presence of cardiac involvement and heart failure connotes the worst prognosis. Recent data from cardiac MRI suggests that about 3/4 of patients with AL amyloidosis have cardiac involvement.

What are the common manifestations of

AL amyloidosis?

Patients most frequently present with signs and symptoms of cardiac or renal disease. Proteinuria is a common initial finding, often associated with nephrotic syndrome and severe edema.

Symptoms of heart failure, such as dyspnea on exertion or at rest and orthopnea are also common. These may be accompanied by signs of right heart failure such as peripheral edema.

The patient may complain of chest discomfort or chest pain, both typical and atypical of angina-like pain. This may be related to impaired myocardial flow reserve associated with small vessel perivascular involvement even in the absence of significant occlusive epicardial coronary stenosis. An elevated troponin level is common suggesting myocyte necrosis. Although the direct cause of necrosis is not known, direct myocyte toxicity by the amyloid proteins or small vessel ischemia may be playing a role.

A patient may present with varying types of arrhythmias. Atrial fibrillation is common. Sudden death is a mode of demise in patients with AL or any cardiac amyloidosis thought due to cardiac electromechanical dissociation or ventricular arrhythmias. Syncope and dizziness are common manifestations and may be due to either arrhythmias or autonomic neuropathy.

Less than 5% of patients with light chain amyloidosis involving the heart have isolated cardiac involvement and it is the presence of associated non-cardiac symptoms that will point to a systemic disease rather than a purely cardiac pathology. Systemic manifestations include weight loss, easy bruising, brittle and slow-growing nails and periorbital purpura. A subtle change in voice, such as hoarseness may occur and be related to vocal cord involvement. Macroglossia or enlargement and stiffening of the tongue is soft tissue involvement of amyloidosis that occurs only in the AL type of amyloidosis. In advanced cases, this may interfere with swallowing, eating or breathing. Other soft tissue in-

involvement includes lymph nodes, salivary glands which may present as submandibular swelling, carpal tunnel syndrome, nail dystrophy, and amyloid arthropathy.

Gastrointestinal manifestations include right upper quadrant discomfort either from chronic passive hepatic congestion or hepatic amyloid infiltration (often massive). Decreased or increased bowel motility may occur with autonomic neuropathy.

Peripheral nerves are often affected and patients may present with paresthesias of peripheral sensory nerves and occasionally with motor neuropathy. Signs of autonomic neuropathy include: dizzy spells and syncope due to orthostatic hypotension, gastric atony, diarrhea or constipation, and impotence. On occasion, a previously hypertensive patient on multiple blood pressure medications may report spontaneous resolution of hypertension at the time of presentation.

The presence of abnormalities in two or more organ systems often leads the physician to consider the diagnosis of amyloidosis.

Key Summary Point 1: It is essential that a patient presenting with symptoms and signs of heart failure be investigated for accompanying systemic manifestations that will provide clues as to the presence of AL amyloidosis. In particular, a history of carpal tunnel syndrome or surgery for carpal tunnel syndrome, orthostatic hypotension or dizziness, reduced need for antihypertensive medications, hoarseness or change in voice, tongue enlargement and skin changes should alert a physician to rule out AL amyloidosis.

What are the pertinent physical examination and cardiac findings in AL amyloidosis?

Signs of heart failure include jugular venous distension, peripheral edema, ascites, pulmonary crackles and signs of pleural effusion. A right ventricular S3 sound may be heard suggestive of right ventricular dysfunction. Because of atrial infiltration and dysfunction, it is uncommon to hear a fourth heart sound. Blood pressure is often low and orthostatic hypotension is common.

Hepatomegaly is common and if due to amyloid infiltration the liver can be hard but non-tender, in contrast to a firm and tender liver when due to chronic passive congestion. As mentioned previously, tongue enlargement, submandibular swelling and nail dystrophy may be seen in some patients.

Perhaps the most important clue to the diagnosis of cardiac amyloidosis is the combined finding of low voltage on electrocardiogram (defined as <5 mm in height in all limb leads, Figure 1) in the setting of left ventricular thickening on echocardiography. It is essential that echocardiographic findings of left ventricular thickening and diastolic dysfunction, especially with concomitant pericardial and pleural effusion be paired with evaluation of the electrocardiogram to determine if the thickening is due to left ventricular hypertrophy (e.g. due to hypertensive heart disease or hypertrophic cardiomyopathy, associated with increased ECG voltage) or due to myocardial infiltration (such as amyloidosis, with low voltage ECG). This singular act will lead to the earlier diagnosis of amyloidosis.

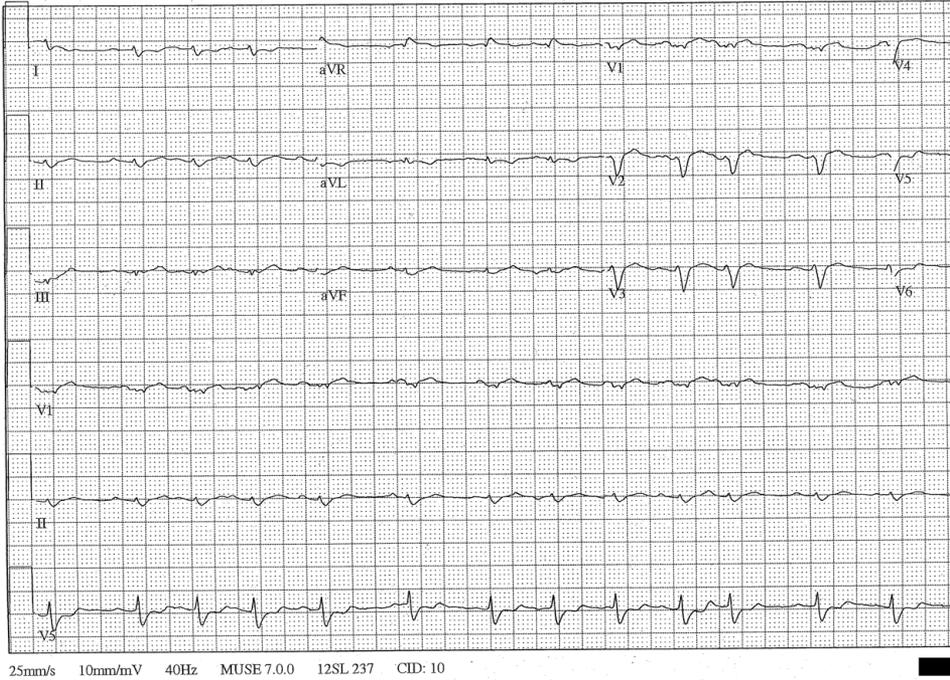


Figure 1. Typical electrocardiogram of a patient with amyloidosis with cardiac involvement demonstrating low limb lead voltages and pseudoinfarct pattern.

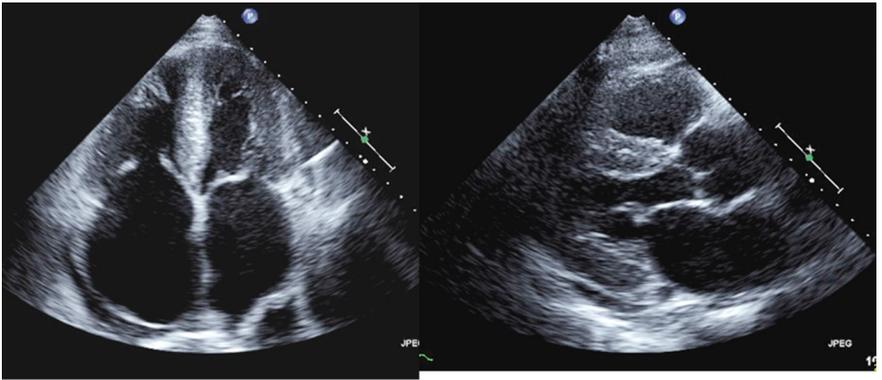


Figure 2. Typical echocardiographic findings demonstrating thickening of the left ventricle and valves, atrial enlargement and presence of pericardial effusion.

Echocardiographic findings include ventricular thickening, small cavity size, significant or advanced (i.e. restrictive filling) diastolic dysfunction and often preserved or hyperdynamic systolic function (although left ventricular ejection fraction may be impaired in more advanced cases). The previously described granular sparkling myocardial appearance on echocardiography is often not helpful because it is very subjective and because similar features are commonly seen with the advent of harmonic imaging on echocardiography. The valve leaflets, atria and atrial septum may appear thick due to amyloid infiltration. Important concomitant clues usually not associated with hypertensive heart disease but are common in light chain amyloidosis include the presence of pericardial and pleural effusion.

Magnetic resonance imaging demonstrates structural findings similar to echocardiography. In addition, the presence of cardiac amyloid infiltration is demonstrated by the presence of enhancement of the myocardium (as well as atria and valves) following gadolinium injection (late gadolinium enhancement) (Figure 3). Gadolinium is an extracellular contrast agent that attains a high volume of distribution in myocardial regions where myocytes are replaced or displaced by infiltrates, fibrosis or inflammation. The

pattern of signal enhancement is often diffuse, ranging from sub-endocardial to transmural. Unique to cardiac amyloidosis versus other cardiomyopathies, the “null point” (or the inversion time needed to suppress the signal) of the myocardium is very close to or may even precede that of the blood pool, signifying high volume of distribution of gadolinium in the myocardium. The presence and pattern of late gadolinium enhancement on MRI has been shown to have high sensitivity and specificity in diagnosing cardiac involvement in LC amyloidosis with myocardial biopsy as the gold standard.

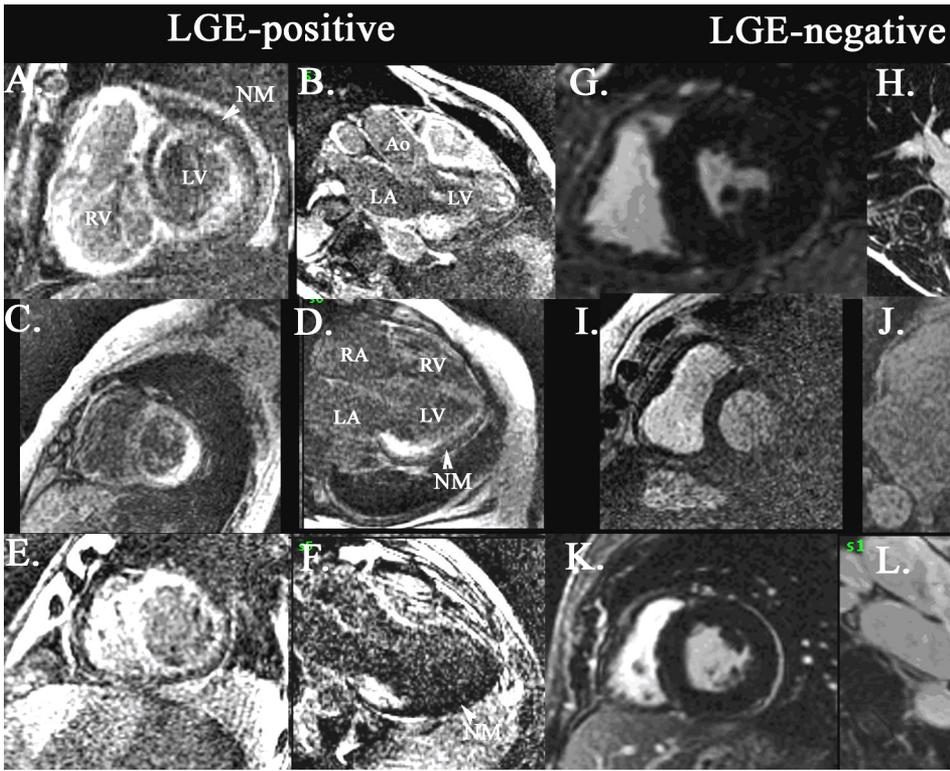


Figure 3. Post-gadolinium MRI images showing late gadolinium enhancement in light chain amyloidosis patients with cardiac involvement (A-F). AL patients without cardiac involvement had no myocardial enhancement (G-L). Reprinted with permission from Migrino RQ, et al. BMC Med Phys. 2009.

Blood examination may show elevated troponin as a result of myocyte necrosis. There may be elevated brain natriuretic peptide (BNP) or N-terminal prohormone BNP (NT-pro BNP). Both findings have been associated with adverse prognosis. Liver involvement may lead to elevated aspartate and alanine transaminases. Alkaline phosphatase may be elevated with liver and bone involvement. Renal involvement may show elevated creatinine and reduced glomerular filtration rate. Anemia may be due to renal dysfunction or due to concomitant multiple myeloma.

Key Summary Point 2: In a patient presenting with symptoms or signs of heart failure, echocardiographic findings of thickening of the left ventricle, diastolic dysfunction, atrial enlargement and pericardial effusion in conjunction with low voltages on electrocardiogram should prompt further definitive testing for cardiac amyloidosis.

What are the definitive tests to diagnose AL amyloidosis?

Several tests are important in making the diagnosis of AL amyloidosis. First a tissue biopsy positive for amyloid deposition by Congo red staining is necessary, with confirmation of the presence of kappa or lambda LCs in the deposit by immunohistochemistry or mass spectrometry analysis. Secondly, the presence of monoclonal light chain production in the bone marrow confirms the systemic AL nature of the disease. The tests required are bone marrow biopsy, serum and urine immunofixation electrophoreses, and free light chain analysis of serum.

Tissue diagnosis can be obtained from any involved organ. Frequently an abdominal fat aspirate is the first test because it is relatively non-invasive and is positive in >70% of patients with AL amyloidosis. If that is negative, a site suspected of disease is sampled next, such as kidney or endomyocardial biopsy both as-

sociated with some (although low) degree of risk, but nearly 100% likely to be positive.

The biopsy in amyloidosis demonstrates typical apple-green birefringence on *Congo red stain* under a polarizing microscope (Figure 4). A more specific stain for amyloid is *Alcian blue stain*. *Electron microscopy* will demonstrate extracellular non-branching fibrils with a diameter of 7.5-10 nM arranged in sheets. These techniques will demonstrate amyloid but will not identify the protein type composing the deposit. It is important for the pathologist to perform immunohistochemical examination (immunofluorescence and/or immunoelectron microscopy) to determine if the protein composition of the amyloid deposit is either kappa or lambda LC. If the composition of the amyloid proteins does not suggest LCs and if there is no corroborating evidence of monoclonal increase in LC in the serum or urine, one should consider genetic testing to rule out other forms of amyloid such as ATTR or rare familial amyloidoses.

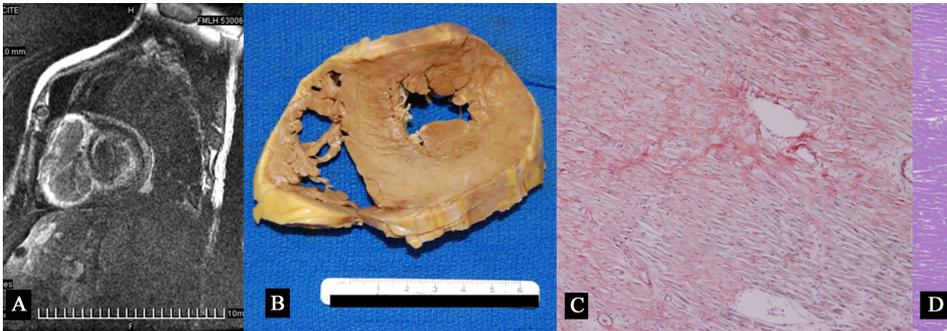


Figure 4. A Cardiac MRI showing diffuse subendocardial late gadolinium enhancement in the left ventricle and diffuse enhancement in the right ventricle. B. Autopsy of the heart showing thick walls. C. Hematoxylin eosin staining showing amyloid deposits in the interstitial space. D. Congo red staining demonstrating interstitial and perivascular amyloid deposits. Reprinted with permission from Migrino RQ, et al. BMC Medical Physics 2009.

In addition to a positive tissue biopsy, there must be corroborating evidence of clonal overproduction of the same type of immunoglobulin light chains. Serum and urine immunofixation electrophoreses, more sensitive tests than protein electrophoresis, should be performed. Serum *free light chain assay* is a simple, sensitive and quantitative test to detect large amount of LC, presumed to be monoclonal. In most cases of AL amyloidosis, the serum free lambda or free kappa LC level is elevated. The burden of serum free light chains is one of the most important prognostic factors in this disease. Because renal dysfunction causes elevated levels of lambda and kappa LCs, it is important to examine the kappa: lambda ratio in addition to absolute values to determine the presence of plasma cells producing clonal LC. A ratio of <0.26 strongly suggests plasma cells producing lambda free LCs and a ratio >1.65 suggests clonal kappa LCs.

Finally, bone marrow biopsy is important to identify increased numbers of plasma cells and to determine clonal production of kappa or lambda LCs by plasma cells using immunoperoxidase staining.

Key Summary Point 3: Serum free LC assay is a sensitive and simple initial test if one is suspicious of AL amyloidosis. This should be routinely ordered in the proper clinical setting (heart failure, left ventricular thickening, and low voltage on electrocardiogram). Abdominal fat pad biopsy is a simple procedure for initial histologic examination for amyloid. Aside from Congo red and Alcian blue stain, one should consider electron microscopy and immunohistochemical examination to increase the sensitivity as well as determine if an immunoglobulin LC comprises the amyloid deposit. If no other accessible tissue source confirms amyloidosis, endomyocardial biopsy may be considered.

How do you treat AL amyloidosis?

The definitive treatment for AL amyloidosis is *removal of plasma cells* producing the immunoglobulin light chains. Clearance of circulating light chains is associated with clinical improvement and prolonged survival. High dose chemotherapy may be offered followed by autologous stem cell transplantation (HDM/SCT) to replace bone marrow cells. However, patients with advanced cardiac or significant multiorgan involvement are often too ill for this aggressive treatment. There are a number of less aggressive oral and intravenous drug options available and in clinical trials at amyloidosis centers. Various chemotherapy regimens may include melphalan, dexamethasone/prednisone, thalidomide or cyclophosphamide, lenalidomide, velcade, or newer novel agent.

Supportive treatment is offered for heart failure symptoms and signs. Diuretics are used to treat fluid overload. Thoracentesis and paracentesis may be required for significant pleural effusion and ascites. Medical treatment of heart failure is often difficult in these patients because of borderline blood pressure and orthostatic hypotension. Therefore, standard heart failure regimens such as beta blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, aldosterone blockers may be utilized but with caution. In advanced cases, inotropic agents are utilized to maintain adequate cardiac output. Digoxin binds avidly to myocardial amyloid fibrils thus increasing the risk of toxicity.

Because ventricular arrhythmias are common in amyloidosis, automated implantable cardiac defibrillator (AICD) treatment with or without biventricular pacing may be considered. There are no specific guidelines on AICD treatment for light chain amyloidosis and clinical practice currently utilizes guidelines used for nonischemic cardiomyopathy. It is also not clear whether routine AICD implantation improves survival in LC amyloidosis, especially since a cause of death may be electromechanical dissociation which AICD is not expected to address.

Because of the increased risk of thromboembolism in LC amyloidosis, anticoagulant therapy is strongly recommended in patients with atrial fibrillation and some experts recommend consideration of routine anticoagulation in patients in sinus rhythm at high risk for thrombus formation such as subjects with poor atrial function determined by transthoracic or transesophageal echocardiography.

In advanced cases, cardiac transplantation is an option, particularly if other organ function is good and the patient is otherwise eligible for HDM/SCT, a treatment that provides sustained benefit. In specialized centers, there have been encouraging survival data on LC amyloidosis patients undergoing cardiac transplantation (including extended donor transplantation utilizing donor hearts not ideal for traditional transplantation) followed by chemotherapy 6 to 12 months later to abolish plasma cell production of amyloidogenic light chains.

Key Summary Point 4: Because treatment of LC amyloidosis is different from other forms of amyloidosis, it is important to determine the nature of the protein comprising the amyloid deposits. Chemotherapy to eradicate the plasma cell dyscrasia is the mainstay of treatment for AL amyloidosis. HDM/SCT is often considered first if the patient is well enough to undergo aggressive treatment, however many other options are now available or in clinical trials with promising results.

What is the prognosis of AL amyloidosis patients?

The prognosis of a patient with AL amyloidosis has dramatically improved over what it was 20 years ago when survival was 1-2 years and worse if the patient had cardiac involvement. Studies have demonstrated that clearance of circulating LCs by HDM/SCT is associated with long-term survival and in some cases apparent cure. Where complete eradication of the clonal LC is not accomplished by HDM/SCT, long-term treatment benefit is still noted. Many of the less aggressive treatments as initial therapy or as

second line treatment are providing extended benefits for patients. At the present time, treating physicians using major and supportive therapies are changing the outlook for AL amyloidosis to that more like treatment of a chronic disease.

Key Summary Point 5: In light of the adverse prognostic implication of LC amyloidosis especially if left untreated, it is essential that clinicians maintain a high level of suspicion for the disease in patients presenting with similar clinical syndrome.

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