

Kappa Light-Chain Primary Amyloidosis Associated with End
Stage Renal Disease and One Patient's Journey

BY:

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INTRODUCTION

Irene Dias, a 50-year-old female, was diagnosed with primary amyloidosis of the immunoglobulin kappa light chain and end stage renal disease (ESRD) (1). Simply put, amyloidosis is a group of diseases characterized by the abnormal accumulation of amyloid proteins in tissues (1). There are three major types of amyloidosis: primary, secondary and hereditary. Although they share the name “amyloidosis”, these diseases are all extremely different from each other.

Primary amyloidosis (AL) is the most common type in the United States, resulting from plasma cell dyscrasia, an abnormality of the blood, which is characterized by increased production of immunoglobulin light chain (AL) or heavy (AH) chains and their deposition in one or more organs of the body (2, 3). The irregular protein deposits are caused by the ability of the light chains to form beta-pleated sheets (4). The end result is organ failure. The organs with highest risk in AL are the heart, kidneys, nervous system, and gastrointestinal tract. Symptoms of amyloid deposits can present themselves as fullness of stomach, dizziness upon standing, weight loss, diarrhea, enlarged tongue, numbness of arms and legs, protein in the urine and kidney failure (5). AL can occur with and is similar to multiple myeloma in that it is also a blood-associated disease. Therefore, the most effective treatment option has been high-dose intravenous melphalan, a chemotherapy drug, among a class of alkylating agents, that helps to slow the production of plasma cells by weakening them, followed by autologous peripheral blood stem cell transplant (HDM/SCT)...This and more treatment options will be discussed in detail later.

Secondary amyloidosis (AA) is the main type of amyloidosis in the developing world. It is caused by chronic infection, which is more apparent in developing countries, or inflammatory disease such as rheumatoid arthritis. In this case the serum protein precursor, SAA, is upregulated causing an incomplete proteolytic digestion producing the amyloid A protein. The amyloid is then irregularly deposited throughout the body's tissues. AA can be accompanied by assorted symptoms because the symptoms are caused by both inflammation and the amyloid A deposits. The symptoms include fatigue, protein in urine and oedema. The underlying chronic infection or inflammatory disease must be treated pharmacologically or surgically to prolong patient life (2,5).

Lastly, hereditary amyloidosis (ATTR) is the rarest of the three. ATTR is associated with mutations in this transthyretin (TTR) gene. The phenotype is autosomal dominant. Due to the dominance, the child only needs one affected gene from either parent to have this disease. TTR is a protein manufactured in the liver. 100 different mutations of this protein alone have already been shown to cause ATTR. TTR forms a tetramer that is responsible for thyroid hormone transport and for binding of retinol. Dissociation of the tetramer leads to the misfolding and release of monomers that deposit in organs and irregularly build up. ATTR is often misdiagnosed as AL because involvement of the nervous

system and gastrointestinal tract cause similar symptoms: dizziness upon standing, numbness in arms and legs, and diarrhea. The best-known treatment is liver replacement to slow the production of TTR protein (2,5).

Any form of amyloidosis (AL, AA or ATTR) is very rare and extremely life threatening. There is no cure. Patients have an average life expectancy of about 1 to 1 ½ years from the time of diagnosis. However, with successful treatment a patient's life may be extended up to an average of 6 years.

CURRENT DIAGNOSTIC STANDARDS

AL is commonly misdiagnosed initially. Unfortunately, the testing process can be extremely painful. Irene Dias originally went to the doctor's for a routine physical exam and presented with high cholesterol. Her cholesterol had jumped from 200 at the previous years physical to 400, and then 500 a few months later. Shortly after, her first symptoms appeared: one pulmonary blood clot, a blood clot in her right calf, extreme edema and fatigue. Irene had points where she did not even have the strength to get off the couch for several days. She was hospitalized for 12 weeks between Dominican and UCSF cancer center, initially being diagnosed with Nephritic syndrome due to the high levels of protein in her urine. After many urine and blood protein level exams, CAT scans, and kidney biopsies she was ultimately diagnosed with AL. Due to the massive deposits in her kidney she was consequently also diagnosed with ESRD, a condition in which the kidney fails to excrete waste and regulate urine and nutrient balance. The final stage of diagnosis was to type the amyloid and to determine the organs affected. However, the organs affected can always change, frequently increasing in number. In Irene's case, bone marrow and kidney biopsies, as well as ultra sounds and x-rays determined that the amyloid kappa light chain is deposited chiefly on her kidneys, GI tract and liver (1).

To determine a possible amyloidosis case preliminary tests are a necessity. The observations of protein levels in blood and urine compared can easily distinguish an imbalance. Whereas, elevated protein levels in the urine is a sign of amyloidosis. The ratio of κ to λ light chains can be compared from both the blood and the urine. If the protein level of one or the other is much higher, there could be a problem in that protein's production. X-rays and CAT scans are able to pictorially identify protein buildups by showing unknown structures in organ tissues. Finally, a biopsy is needed to confirm the prognosis and determine the type of amyloid that needs to be dealt with.

Amyloids are caused by protein misfolding that results in β -pleated sheet formation (2). In AL these amyloids are λ and κ immunoglobulin light chains which, are not bound to heavy chains. They are free-floating and able to deposit wherever (Figure 1) (6). Each immunoglobulin is composed of 2 identical heavy chains and 2 identical light chains. Every light chain has a variable and constant region. The variable region can have different misfoldings that cause different types of amyloids, having a tendency to deposit in different tissues (2). Therefore, the type of amyloid and the organs affected is highly variable from patient to patient.

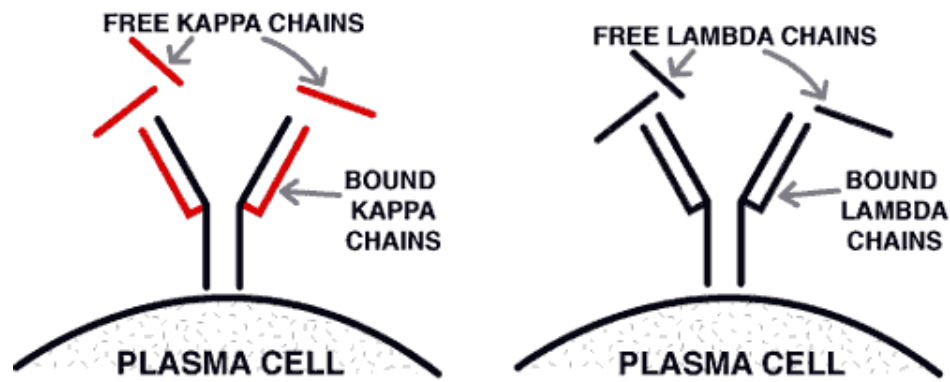


Figure 1. Free light chains in the blood (6)

Renal biopsies are very commonly used since the kidney is typically highly affected in AL. Amyloids can be found deposited in the glomerular capillary walls and the renal vessels of the kidney (7). Once a biopsy is taken further microscopic tests must be done to type the amyloid. The current gold standard for all types of amyloids, even though it is not necessarily the most sensitive, is the Congo red staining technique (2). The Congo red stain has a high affinity for free-floating amyloid proteins and identifies an amyloid under polarized light or electron microscopy with a green birefringence (Figure 2).

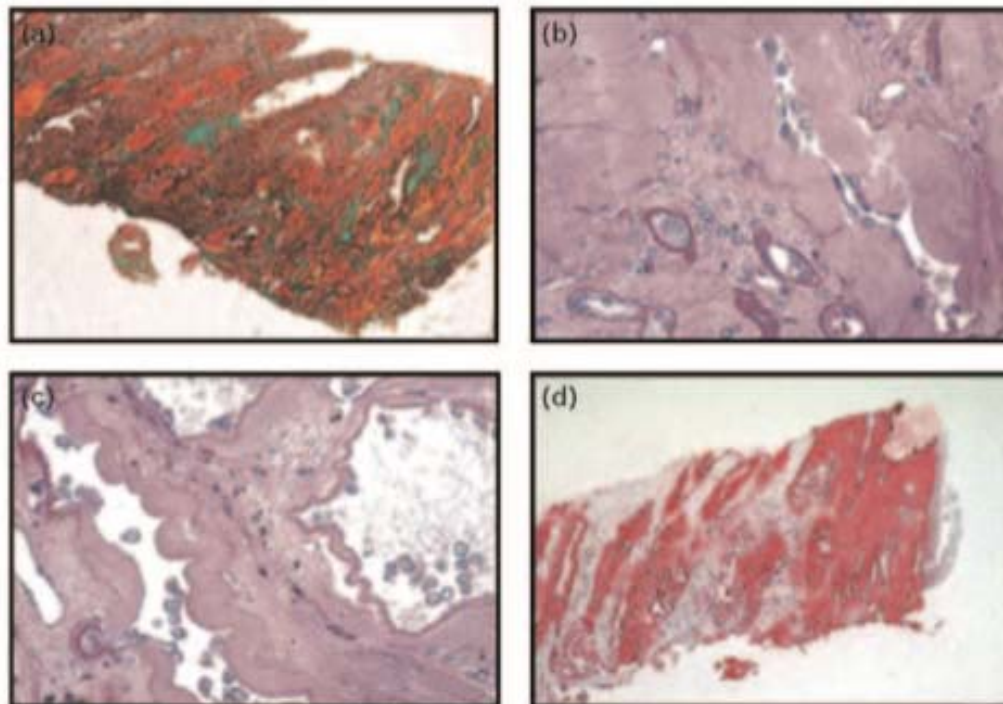


Figure 2. Amyloid detection in various renal biopsies using Congo red staining technique (2)

Immunohistochemical amyloid typing is also used, but only has a 38 to 87% success range. The variable region poses a problem in the use of antibody-

based techniques because it is difficult to commercial antibodies that are reactive with all amyloid types (2). However, a sensitive antibody can be marked with an immunofluorescence and easily show amyloid presence within biopsy (Figure 3).

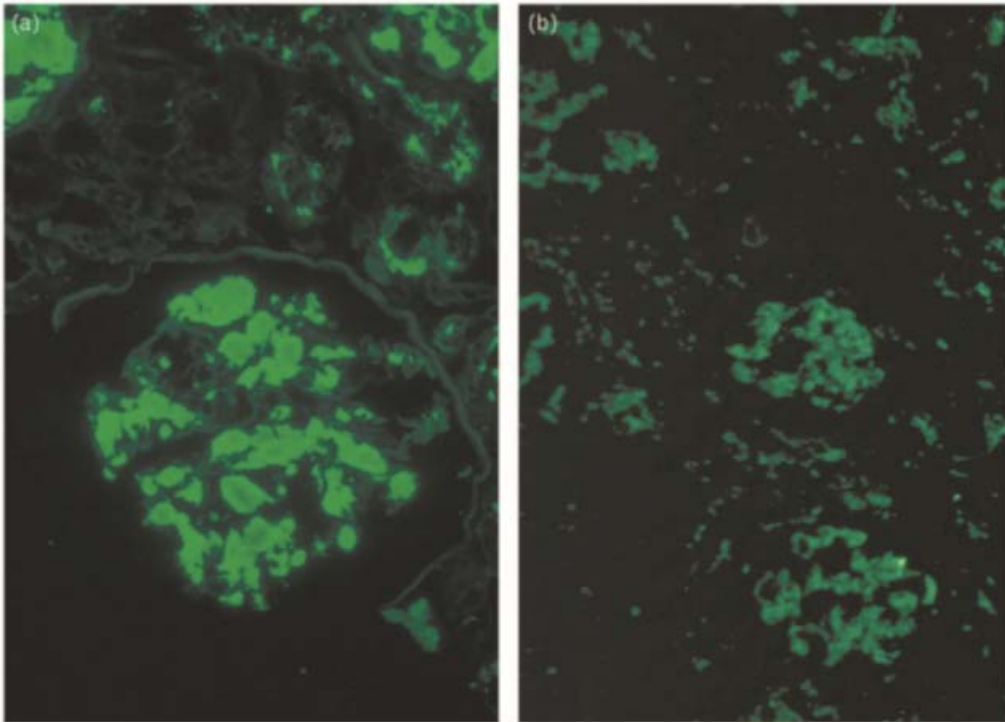


Figure 3. Direct immunofluorescence stain of various kidney biopsies in a patient with AL (2)

All AL amyloids, in each of these pictorial techniques, are characterized as non-branching, randomly oriented fibrils measuring 9-11 nm in thickness (7). Other techniques in antibody-base typing, electron microscopy and western blotting are in the testing phases for sensitivity in clinical use.

HIGH-DOSE MELPHALAN WITH AUTOLOGOUS STEM CELL TRANSPLANT

Although there is no cure for AL aggressive treatment can greatly extend a patient's life. For many patients it might be a question of whether or not the pain and sickness of the treatment, along with the 15% chance of death, is worth a possible few extra years here on Earth. For Irene it was well worth the risk. Immediately after diagnosis she began high-dose intravenous melphalan followed by an autologous peripheral blood stem cell transplant. UCSF harvested Irene's stem cells and froze them. 2 days later she began treatment with oral high-dose melphalan and finalized the treatment with her frozen stem cells being retransplanted. This treatment process was not easy and caused Irene 2 trips to the ICU, two detached retinas and extreme blurred vision and a high bleeding risk because of blood thinners treating the blood clots. The toxicity

was very high and remained that way for about a year with nausea and vomiting due to the organ damage from the disease (1).

AL can occur with multiple myeloma and the causes of both diseases originate in the plasma cells. The most common and effective treatment for multiple myeloma is currently oral chemotherapy drugs, mainly melphalan and prednisone. Therefore, following in the footsteps of multiple myeloma, the first and most obvious treatment available for AL was low-dose oral melphalan and prednisone. However this approach only increased the median of survival to about 17 months. Complete hematological responses (“elimination of the underlying plasma cell dyscrasia”) rarely occurred (3). Something better was needed.

High-dose intravenous melphalan chemotherapy with autologous blood stem cell transplantation (HDM/SCT) is currently the most successful and most aggressive treatment for patients with AL. In 1996, a clinical group was put together at Boston University to develop high-dose chemotherapy protocols for AL. The initial treatment protocols were tested on five patients, three of them achieving complete hematological responses and all five regaining function of organs damaged by the amyloid. There were multiple tests group organized and the largest consisted of 200 patients. 152 of these patients survived for at least one year after the completion of treatment with good hematological progress (Table 1). 27 of these patients were over the age of 65. Only 2 died due to treatment toxicities, proving that elderly patients can tolerate HDM/SCT (3).

Table 1. (a) Frequency of toxicity due to treatment and (b) the survival of 152 patients for the first 4 years after treatment (11)

(a)			
<i>Toxicities</i>	<i>Number of patients (of total group of 152)</i>		<i>%</i>
Nausea or vomiting	70		46
Diarrhea	70		46
Mucositis	70		46
Pulmonary edema	20		13
Peripheral edema	29		19
Gastrointestinal bleeding	11		7
Non-gastrointestinal bleeding	11		7
Hepatic	21		14
Renal	27		18
Metabolic	72		47
Sepsis	25		16

(b)			
	<i>2 years (%)</i>	<i>3 years (%)</i>	<i>4 years (%)</i>
Overall	65	60	60
Non-cardiac	85	85	85
Hem CR	91	91	91
Non-CR	80	80	80
Cardiac	49	40	40
Hem CR	56	43	43
Non-CR	41	38	38

ESRD poses another complication to treatment options because of the requirement for dialysis treatment for ESRD. 12 patients having this complication were treated in the above study. There was no difference in survival rate between AL patients with or without ESRD; however patients who had ESRD were more susceptible to treatment toxicities. There were also 26 patients with high-risk cardiac disease treated (with an above average intraventricular septum thickness of >15mm). 14 of these patients died before the end of treatment or within one year after, suggesting a need for higher selectivity when dealing with patients with amyloid-cardiac involvement (3).

Even after HDM/SCT, Irene continues dialysis injections 3 days a week for her ESRD (1). In patients with ESRD, the kidneys have lost the ability to properly filter the blood. Therefore, dialysis treatment offers a chemical solution, dialysate, to maintain proper blood filtration by drawing fluids and toxins out of the bloodstream and supplying electrolytes to the bloodstream (8).

LIVING DONOR KIDNEY TRANSPLANT

Amyloidosis is a common cause of ESRD (8). Although HDM/SCT is currently the most effective treatment for AL, it does not offer any help for kidney failure. An eight patients study, presented in the American Journal of Transplantation, tested a treatment option including live donor kidney (KTx) and autologous stem cell transplantation (ASCT) for AL patients with high renal involvement (4). This treatment could be a secondary option for a patient such as Irene who has been treated successfully for AL, but is left with chronic ESRD. It could allow her to stop dialysis by curing the kidney failure and therefore, extending her life expectancy. In this study all patients were between 51 and 65 years of age and renal AL was diagnosed by renal biopsies. The biopsies were then stained with Congo-red to determine amyloid type. Finally, the stage of the patient's AL was determined by bone marrow biopsies and urine protein excretion. Kidney donor candidates underwent multiple consultations along with full blood and urine panels, chest x-rays, electrocardiograms, tissue typing, measurement of GFR and assessment of renal anatomy by CT. The GFR, Glomerular filtration rate, describes the filtering capacity of the kidneys depending on a person's gender, age and size. This test compares the serum creatinine levels in the patient's urine to the levels in their blood to see how well the kidney is able to clear creatinine from the body. For kidney transplantation immunosuppressive pharmaceuticals were given orally to each patient. Oral immunosuppressive treatment was conducted with regimens of tacrolimus, cyclosporine or sirolimus with mycophenolate mofetil and prednisone. This type of immunosuppressive treatment is usually used before and after organ transplantation to reduce the efficacy of the patient's immune system and prevent organ rejection. (Cyclosporine and tacrolimus are typical immunosuppressive pharmaceuticals used in conjunction with organ transplantation.) The patient must first have a successful kidney transplant and acceptable renal function

(GFR greater than 5%, glomerular filtration rate calculated by blood creatinine tests, age, gender and race) before receiving autologous stem cell transplant (4).

6 out of the 8 test patients lived, however only 5 were able to proceed with autologous stem cell transplant (ASCT) (Figure 4). Infections cause a high mortality rate in patients post-transplantation (8), which killed one of the patients. A second patient did not undergo ASCT, due to kidney transplant complications, but was still able to live with stable kidney function. This shows, along with other studies, that failing kidney function can be treated with KTx in AL patients, such as Irene, who have been treated for AL (8, 4). ASCT of the other 5 patients was conducted within the following year and all survived with no serious complications and stable kidney function.

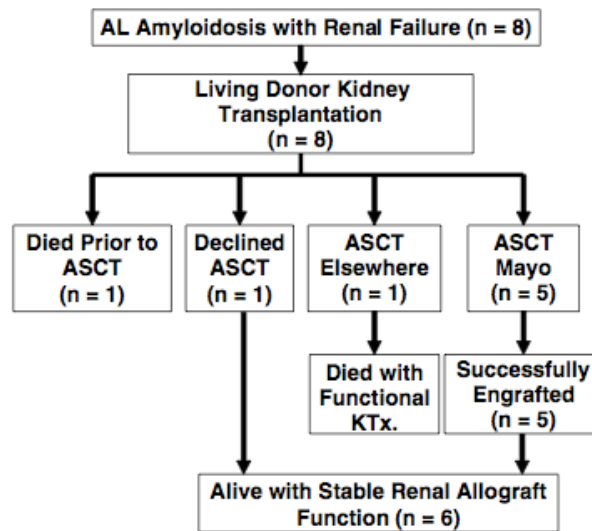


Figure 4. Flow diagram illustrating clinical outcomes of kidney transplantation patients with AL associated with ESRD. ASCT is autologous peripheral blood stem cell transplant and KTx is living donor kidney transplant, where n is the number of patients in that part of the study (4)

These procedures however are not easy on the patient. The patient must heal from both KTx, with hospitalization of 4-5 days followed by immunosuppressive regimens, and ASCT, with hospitalization of 21-59 days. Both of these treatments include multiple tests and biopsies before and after each procedure. Plus this treatment option only works for specific AL patients because it only focuses on the kidney and there have been an increasing number of cases of AL with multiple organ involvement. Patient selection is very important and this treatment is currently most appropriate for AL patients with predominantly single-organ kidney dysfunction. Hopefully, one day there will be this type of treatment option for AL patients in need of different or multiple organ transplantation.

VINCRISTINE, DOXORUBICIN AND DEXAMETHASONE TREATMENT

3 AL patients, 62 to 71 years of age, were diagnosed with nephritic syndrome, a non-specific disease that leads to kidney failure. All were successfully treated with vincristine, doxorubicin and dexamethasone (VAD). VAD is another type of chemotherapy that is also being used as a treatment for multiple myeloma. Its primary use in treating AL was for patients who were turned down as high-risk cases for high-dose melphalan, mainly due to the decreasing function of two or more organs. Recent reports also show that it even might be useful in preparing a patient for treatment with high-dose melphalan to ensure a more successful treatment. VAD allows for rapid reduction of pathogenic plasma cells and has no negative effects on mobilization of hematopoietic stem cells, thus allowing cell production to continue normally while killing the plasma cells responsible of the amyloid production (9).

Just as any other chemotherapy, VAD has toxic effects. The vincristine and doxorubicin can cause cardiac toxicity and neuropathy, dysfunction of neurons. Dexamethasone can cause severe fluid retention. None of these symptoms occurred to any harmful degree in these patients. After 1 or 2 cycles of VAD all three patients' amyloid was found to be nonexistent by serum and urine tests. κ and λ serum levels were reduced to normal leading to complete hematological remission. Although more clinical studies are necessary, this treatment should be considered an option (9).

MAINTINENCE OF AL AND CONCLUSION

For patients diagnosed with AL, death is inevitable, but maybe one day there will be a cure. In the meantime, however, for patients like Irene the difficulties of experimental treatments are worth the possibility of a longer life. Holding her head high through this process, Irene has learned that God's grace is sufficient and she holds onto her faith and family tightly (1). Even after HDM/SCT Irene continues to search for further treatment. Three days a week Irene is in the hospital for dialysis treatment and later this month she will find out if she is a candidate for a living donor kidney transplantation. Her treatment will never be over.

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