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Renal transplantation in amyloidosis and MIDD

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1. ABSTRACT

Amyloidosis and monoclonal immunoglobulin deposition disease, though rare entities, can wreak havoc on the architecture and functioning of the kidneys. These diseases have a predilection to cause severe renal dysfunction leading to end stage renal disease (ESRD). In recent years, the available treatments for these diseases have expanded and afflicted patients are living longer, but with advanced kidney disease. Because of the complex nature of the pathophysiology and treatment of these diseases, it can be very challenging for a clinician to determine whether or not it is appropriate to refer an affected individual for kidney transplantation.

2. INTRODUCTION

Amyloidosis is the clinical syndrome that occurs when a protein abnormally folds, aggregates and deposits into various tissues. It is usually a systemic disease that can often involve the heart, kidneys, GI tract, liver, peripheral nervous system, skin, joints, thyroid and soft tissues. There are a number of potentially amyloidogenic proteins including light chains, heavy chains, serum amyloid A (SAA), beta-2microglobulin, lysozyme, fibrinogen A-alpha, gelsolin, transthyretin, cystatin C and various apolipoproteins (Table 1) (1). Amyloidogenic proteins have a distinct pattern of organ damage, with kidney involvement being very common among certain types, often resulting in end stage renal disease (ESRD).

The first kidney transplant performed in a patient with systemic AL amyloidosis and ESRD took place in 1967 and the allograft only functioned for twelve days. At that time there were few treatments available for amyloidosis and very few effective options for immunosuppression (2). Kidney transplantation has now become a more viable therapy for ESRD secondary to amyloidosis or in the modern era of successful treatment of plasma cell dyscrasias.

Table 1. Types of systemic amyloidosis

Disease	Precursor Protein	Amyloid Protein	Organ Involvement
AL amyloidosis	Monoclonal Ig light chain	AL	Kidney, heart, liver, gastrointestinal tract, nervous system, soft tissue, spleen, thyroid, adrenal gland, etc.
AH amyloidosis	Monoclonal Ig heavy chain	AH	Extremely rare: kidney involvement predominates in the small number of reported cases
AA amyloidosis	Serum amyloid A (SAA)	AA	Kidney, liver, gastrointestinal tract, spleen, autonomic nervous system, thyroid
Transthyretin amyloidosis, Hereditary	Transthyretin (mutant form)	ATTR	Peripheral nervous system, heart, vitreous opacities; kidney involvement is rare
Fibrinogen Aα amyloidosis, Hereditary	Fibrinogen Aα chain	AFib	Kidney, liver, spleen; hypertension is common; kidney involvement is predominantly glomerular
Apolipoprotein AI amyloidosis, Hereditary	Apolipoprotein AI	AApoAI	Kidney (with predominantly medullary deposition), liver, heart, skin, larynx
Apolipoprotein AII amyloidosis, Hereditary	Apolipoprotein AII	AApoAII	Kidney
Lyzozyme amyloidosis, Hereditary	Lyzozyme	ALys	Kidney, liver, gastrointestinal tract, spleen, lymph nodes, lung, thyroid, salivary glands
Gelsolin amyloidosis,	Gelsolin	AGel	Cranial nerves, lattice corneal dystrophy
Cerebral amyloid angiopathy, Hereditary	Cystatin C	ACys	Cerebral vessels
Senile systemic amyloidosis	Transthyretin (wild type)	ATTR	Heart, soft tissue
Dialysis-related amyloidosis	B2-Microglobulin	Aβ2M	Osteoarticular tissue; less common sites are gastrointestinal tract, blood vessels, heart
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3. AL AMYLOIDOSIS

AL amyloidosis is primarily a bone marrow disorder, with the overproduction of aberrant light chains from clonal plasma cells that form beta pleated sheets that circulate to highly trafficked internal organs. The kidney is commonly affected in this condition and manifests disease with nephrotic syndrome and progressive renal failure. A number of studies have shown that the average time from the time of diagnosis to progression to ESRDis 13-35 months (3, 4), with a median survival time from the initiation of dialysis being 39.0 months (5).

Treatment of AL amyloidosis is aimed at ridding the bone marrow of the abnormal plasma cell clone in order to halt the production of light chains by these cells. Until the late 90's, the only treatment available for this disorder was oral melphalan and prednisone. At that time survival was noted to be 51% at 1 year, 16% at 5 years, and 4.7% at 10 years (6). Since then the arsenal of available therapeutics has expanded to include high dose melphalan with autologous stem cell transplant (HDM/SCT), lenalidomide (thalidomide analog), and proteosome inhibitors (bortezimib) (7). At this time there are also some promising trials of pomalidomide, which has been shown to have some success in the treatment of multiple myeloma. Currently, HDM/SCT seems to be the initial treatment of choice for patients that have good overall functional capacity. Of all of the available therapies at this time, HDM/SCT is the most likely to produce a durable complete hematologic response (CR) (7-9). CR is defined as the absence of monoclonal protein in serum and urine by immunofixation electrophoresis, normal serum free light chain ratio, and bone marrow biopsy with <5% plasma cells with no clonal predominance by immunohistochemistry. A partial response (PR) is defined as a greater than 50% reduction in the serum monoclonal protein (when measurable) (10). Recently, a new category was added to CR and PR: very good partial response (VGPR) is achieved when the difference between involved and uninvolved

FLCs is less than 40 mg/L (11). One study showed that the median survival can exceed 10 years for patients achieving CR after HDM/SCT, compared with 50 months for those not achieving a CR. The survival in patients achieving VGPR is intermediate between CR and PR (11).

3.1. Kidney transplantation in AL amyloidosis

In a recent retrospective analysis of 25 patients with AL amyloidosis who underwent kidney transplantation in the UK, median graft survival was 5.8 years with a 5- and 10-year graft survival of 74% and 25%, respectively. No grafts failed from recurrent amyloidosis, despite its presence in 7 of the allografts at a median of 5.9 years after transplantation (12). The median survival after renal transplantation was 89.0 months (5).

Currently we recommend that patients should achieve CR, or at least a very good partial hematologic response (VGPR) to therapy that is durable for at least 9-12 months prior to pursuing kidney transplantation but more studies are required to determine the optimal timing of the renal transplant (13). Pinney *et al*. reported that there was no significant difference in renal allograft survival between patients who were in CR versus patients in PR. They did note, however, that patients who did not have a response (NR; No Response) to therapy prior to renal transplantation had significantly worsened graft survival (NR vs PR: 5.3 vs 8.9 yrs) (12).

A small retrospective study that specifically compared different therapies for plasma cell dyscrasias and the outcomes of allograft and patient survival (HDM/SCT pre-kidney transplantation, HDM- SCT post kidney transplantation, and various nonmyeloablative strategies), showed that overall survival was not different for the 3 groups, but that patients who underwent HDM/SCT post kidney transplantation did have a tendency towards more acute cellular rejections (14).

4. MONOCLONAL IMMUNOGLOBULIN DEPOSITION DISEASES

The clinical presentation of monoclonal immunoglobulin deposition diseases (MIDD) is similar to amyloidosis: it can be suspected in patients with proteinuria and a monoclonal protein in serum and/or urine. MIDD includes light ch ain deposition disease (LCDD), heavy chain deposition disease (HCDD) and light- and heavy-chain deposition disease (LHCDD). In LCDD the light chain fragments (more often kappa than lambda) form granular deposit in a variety of organs including kidney, heart, liver and GI tract without forming amyloid fibrils, and are Congo Red negative (37). Immunofluorescence microscopy is typically strongly positive for the monoclonal light chain. In the less frequent forms, HCDD and LHCDD, short (truncated) heavy chains or light and heavy monoclonal chains cause non-amyloid tissue deposition and biopsy tissue stains positive with anti-heavy chain antibodies on immunoflourescence.

The prognosis of LCDD without treatment is usually poor: the median survival is 18 months - 5 years from the time of diagnosis (38, 39) and the median survival rate of patients with LCDD on dialysis is only 4 years (40, 41). Without treatment all forms of MIDD tend to recur after renal transplant (41-47). Accumulating data in MIDD on chemotherapies used to treat AL amyloidosis or multiple myeloma and stem cell transplantation are promising (48-50) and we have increasing number of patients whose plasma cell dyscrasia is under control but they reach ESRD hence in the need of a new kidney (41, 48, 51).

4.1. Renal transplantation on monoclonal immunoglobulin deposition diseases

Given the uncertainty of outcomes, only a small number of renal transplants had been performed in MIDD patients and no large studies are available to date. Transplants that were done before currently used treatment options became available over the last 10-15 years had very different results than studies that looked at renal outcomes in patients who were successfully treated. Before treatment options were wildly available, LCDD recurrence was between 71% - 86% after renal transplant, strongly suggesting that without treating the underlying hematologic malignancy renal transplantation should not be undertaken (41-47). This was illustrated in a retrospective review of seven patients with LCDD form the Mayo clinic who underwent renal transplantation and their recurrence rate was unacceptably high: the disease recurred after a median of 33.3. (range: 2 to 45) months in 5 of the 7 patients and 4 have died within 3-92 months after transplant. The overall median allograft survival was 37.3 months (vs 101.8 months in the general population). The median survival rate after recurrence was 3.6 years (range, 0.3 to 8.4 years). Only 1 patient was recurrence free after 13 years with normal renal allograft function (45).

However, similar to AL amyloidosis, kidney transplantation should be considered in MIDD patients who have achieved a hematologic complete response. In these patients disease free graft and patient survival was documented in several small studies although with less than 1-4 year follow up (48, 52, 53). Even if there is a recurrence of the hematologic disease, case reports suggest that recurrent LCDD after renal transplantation can be successfully treated with bortezomib rescue therapy (50, 54) or prevented by rituximab (55).

5. AA AMYLOIDOSIS

AA or secondary amyloidosis, is the result of a longstanding chronic inflammatory state that leads to the accumulation of the acute phase protein serum amyloid A (SAA) in various organs. Autoimmune diseases such as rheumatoid arthritis, inflammatory bowel disease, familial Mediterranean fever, chronic infection, and TRAPS syndrome have been implicated in the pathogenesis of this disease. In one series, the duration of symptomatic inflammatory disease before the diagnosis of amyloidosis was 17 years without significant difference amongst the various underlying disorders (15). AA amyloidosis presents with nephrotic syndrome and progressive renal failure. The time to ESRD after diagnosis is usually short: the median time from diagnosis to ESRD is 1.4 years (12).

There is subset of patients that have no identifiable cause even after extensive testing. In one retrospective study of 374 patients, up to 6% had no known identifiable cause for AA amyloidosis (15).

5.1. Kidney transplantation in AA amyloidosis

Prior to undergoing kidney transplantation it is vital to determine co-morbid conditions that would preclude transplantation (advanced heart involvement, etc) and the underlying inflammatory state that is causing the disease. The main focus after renal transplantation is to control the underlying inflammatory process to prevent recurrent amyloid deposition in the allograft. For example, colchicine therapy in patients with familial Mediterranean fever is imperative for good graft survival (16, 17). In one multicenter retrospective study of 59 patients who underwent kidney transplantation, the recurrence rate of renal amyloid was estimated at 14%. It was also noted that the 5- and 10-year patient survival was significantly lower for the AA amyloidosis patients than for the control group of 177 renal transplant recipients (18) (82.5% vs. 94% at 5 years, and 61.7% vs. 83.4% at 10 years). Interestingly, it was noted that there was not statistically significant difference in the overall 5 and 10 year graft survival (sensored for death) (18). In another study that sought to determine an association between SAA levels and transplant outcomes, graft survival (noncensored for death) was 14.5 years in patients with a median SAA value of <10 mg/L, and 7.8 years in those with a median SAA of >10 mg/L (p = ns) (12). SAA is not routinely measured and followed throughout the lifespan of a transplant, but it may be an interesting avenue for further exploration.

6. HEREDITARY AMYLOIDOSIS

The hereditary amyloidoses are a group of diseases that generally result from single point mutation in a number of different proteins. They are divided into neuropathic (transthyretin) variants and non-neuropathic variants. They tend to be inherited in an autosomal dominant pattern with variable penetrance amongst those affected.

6.1. Hereditary transthyretin amyloidosis

Familial transthyretin amyloidosis, also known as familial hereditary polyneuropathy (FHP), is the result of a mutation in the transthyretin (TTR) protein. TTR is a structural protein that transports thyroxine and retinal binding protein (RBP)/vitamin A and is made predominantly by the liver, as well as the retina and choroid plexus (19). Over 100 mutations of aberrant TTR leading to amyloidosis (ATTRm) have been identified at this time. This disorder should not be confused with Systemic Senile Amyloidosis, which is the tendency of wild type TTR to become amyloidogenic and cause cardiomyopathy with increased prevalence in African Americans. ATTRm can present clinically with peripheral and autonomic neuropathy, cardiomyopathy, dysrhythmias, and in some cases nephropathy. The disease typically becomes apparent by the second to third decade of life, but this can be variable depending on the specific mutation. Kidney involvement is usually a late manifestation of the disease and tends to present as proteinuria with progressive renal dysfunction. In one cohort, time between detection of microalbuminuria and overt renal disease was 2 years (20).

Because the aberrant protein mainly comes from the liver, orthotopic liver transplantation (OLT) has been utilized as definitive therapy to prevent progression of end organ damage. There have been a number of combined kidney-liver transplants

in patients with advanced kidney disease. In one series of six patients who underwent liver-kidney transplantation, none had evidence of recurrence of kidney disease 7 years post transplant 21, 22). The explanted livers from these patients can be utilized for domino transplantation in OLT candidates despite their production of aberrant TTR, because they are functionally and anatomically normal. It has been theorized that the recipient of the new liver will not live long enough to experience clinical manifestations of FHP due to its slow progression (23).

6.2. FIBRINOGEN A ALPHA AMYLOIDOSIS

Fibrinogen is a plasma glycoprotein synthesized by the liver and essential for fibrin clot formation (24). There have been six mutations within the c-terminus that have been identified and are known to cause nephrotic syndrome with progressive renal dysfunction (25). Previously this subtype of amyloidosis was considered to be limited to the kidneys, but one recent study identified amyloid in cardiac tissue and peripheral nerves (25).

Gilmore *et al*. followed 72 patients with biopsy proven renal fibrinogen A alpha amyloidosis and found that the median time from presentation to ESRD was 4.6 years, with 44 patients reaching ESRD (26). 10 of these patients underwent kidney transplantation with median follow up of 5.8 years. The estimated median graft survival was 6.7. yr (range 0.9 to 12.2) and three grafts failed because of recurrent amyloid after 5.8, 6.0, and 7.4 years. Because the aberrant protein is produced by the liver, it has now become more commonplace to consider preemptive liver transplant or combined liver-kidney transplantation, but this remains very controversial due to the higher post transplant mortality rate with OLT versus solitary kidney transplantation (27, 28). Stangou *et al* reported that in one study of 9 patients in the UK who received preemptive combined liver-kidney transplant, 7 out of 9 patients were alive at the end of the follow up period (median 67 months) with 1 requiring RRT because of chronic allograft nephropathy, and 2 deaths from post-operative complications from liver transplantation (25, 28).

In another study of 51 patients, the median graft survival among patients with isolated kidney transplant was 7.3 years compared to 6.4 years in those who received combined liver-kidney transplants. Recurrent amyloid was identified in the renal allografts of seven patients, all of whom had isolated kidney transplants, after a median of 4.9 years. No patient with a combined liver kidney transplant developed amyloid in the new renal allograft (12).

6.3. Lysozyme amyloidosis

Lysozyme is a bacteriolytic enzyme that is synthesized in the GI tract by macrophages and hepatocytes. This subtype has been associated with a variety of gastrointestinal symptoms including abdominal pain, nausea, vomiting, diarrhea, hepatic infiltration, GI bleed, malabsorption and weight loss; as well as sicca syndrome, lymphadenopathy and proteinuria (mostly subnephrotic) with the eventual progression to ESRD (29).

In one series of three patients with lysozyme amyloidosis, decline in kidney function was very slow, with the median time from diagnosis to ESRD of 10.6 years. All three received kidney transplants and had excellent graft function at 0.9., 2.9 and 6.2 years post transplant without evidence of amyloid recurrence in the allografts (12). In another case series of 16 patients, 5 reached ESRD, and 3 underwent kidney transplantation. None of them had recurrence of amyloidosis in their grafts at 0.8, 1.8 and 6.6 years after transplantation (29). At this time there are no documented cases of graft failure from lyzozyme amyloidosis in the literature.

6.4. Apo A1 amyloidosis

Apo A1 is a major constituent of HDL and is secreted by the liver and intestines (30). At this time, 14 different mutations have been shown to cause clinical amyloidosis (25). The clinical presentation is widely variable and can involve the liver, kidney, heart, skin, testes, larynx and peripheral nerves (31). The pattern of renal injury is very variable depending on the specific mutation. In addition to nephrotic syndrome and progressive renal dysfunction, a small number of cases have been shown to mainly involve the tubulointerstitium leading to urinary concentrating difficulties, polyuria and only minimal tubular proteinuria. Progression of renal impairment is often very slow.

In one series of 10 patients who underwent kidney transplantation for Apo A1 amyloidosis, 7 out of 10 patients had functioning grafts 9 years post transplant. The authors also noted that the case for combined liver-kidney transplant was weak without evidence of widespread liver disease given the favorable outcomes of isolated kidney transplantation (30).

6.5. Apo A2 amyloidosis

Similar to Apo AI, Apo AII is also a large component of the HDL protein that is synthesized in the liver and intestine. There have only been a few reports in the literature that focus on renal involvement and they have noted that the pattern of kidney injury results in proteinuria and eventual ESRD (32). In one case report, the patient developed ESRD at age 45 and underwent successful cadaveric kidney transplantation with stable graft function over the 9 year follow up period (33).

6.6. Apo AIV amyloidosis

To date there is only one reported case of renal Apo AIV amyloidosis in the literature. Similar to some variants of the Apo AI subtype, renal involvement was confined to the medulla, without evidence of significant proteinuria (34). In our center, we currently have two patients with a similar presentation, who were diagnosed by kidney biopsy during evaluation for CKD of unknown origin. At this time there have not been any reports in the literature of biopsy proven renal Apo AIV amyloidosis patients that have gone on to receive kidney transplants. It is worth considering that this variant may be underdiagnosed because it is typically limited to the renal medulla, which is often not sampled during renal biopsy.

6.7. Gelsolin amyloidosis

Gelsolin amyloidosis, also known as Finnish type amyloidosis, is a rare subtype of hereditary amyloidosis. Patients typically present with lattice corneal dystrophy, progressive neuropathies including involvement of the cranial nerves, and development of cutix laxa (35). Renal involvement has been documented, but it is rare. It can manifest as nephrotic or subnephrotic range proteinuria with progressive renal dysfunction. There has been one case report in the literature of a patient in Iran who underwent successful kidney transplantation for the treatment of ESRD associated gelsolin amyloidosis. At 6 year followup he had no evidence of recurrence of proteinuria or renal dysfunction (36).

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