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COMPREHENSIVE REVIEW

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Plasma cell diseases and organ transplant: A comprehensive review

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Plasma cell diseases are a class of hematologic diseases that are sometimes present as preexisting diagnoses prior to organ transplantation, causative factors leading to a need for organ transplantation, or may occur posttransplant as part of the spectrum of posttransplant lymphoproliferative disorders. Herein, we review the most common plasma cell diseases, both as coexisting with other causes of organ failure, but also as a primary underlying cause for organ failure. In many cases, treatment of the underlying clonal disease may be indicated before proceeding with organ transplant. This review aims to provide current and relevant data regarding the management of these conditions in the organ transplant patient, for transplant providers, and those who take care of these patients.

KEYWORDS

cancer/malignancy/neoplasia, clinical research/practice, heart transplantation/cardiology, hematology/oncology, kidney (allograft) function/dysfunction, kidney (native) function/dysfunction, kidney disease, kidney transplantation, kidney transplantation/nephrology, living donor

1 | INTRODUCTION

The plasma cell dyscrasias and plasma cell neoplasms comprise a heterogeneous group of disorders characterized by a clonal, often disease-causing plasma cell population. The most common such disorders encountered by providers include plasma cell neoplasms such as multiple myeloma (MM), and plasma cell dyscrasias including smoldering myeloma (SMM), monoclonal gammopathy of undetermined significance (MGUS), immunoglobulin light-chain (AL) amyloidosis, and light-chain deposition disease (LCDD). These diseases are encountered prior to organ transplantation, and may also be diagnosed post-organ transplant as part of the spectrum of posttransplant lymphoproliferative disorders (PTLD). The pretransplant setting is the most frequent time that patients and providers will encounter and manage the disease-related risks and prognoses—and as such, this setting will be the focus of much of this review.

Our goal is to review the existing literature pertaining to these conditions in organ transplant, and create a guide for providers in this setting, using an evidence-based approach. Specifically, we aim to review the available literature regarding these disorders in organ transplant, and provide expert recommendations on management of these disorders in the organ transplant patient population. Our approach to determining levels of evidence is described in greater detail to follow.

2 | LEVELS OF EVIDENCE

In order to apply rigorous criteria to the available data, we have elected to use the 2011 Oxford Centre for Evidence-Based Medicine Levels of Evidence.[1] This ranking scheme was devised to help clinicians and researchers answer clinical questions quickly. They are not, however, intended to provide a recommendation—they are intended to support a treatment or intervention's recommendation, but cannot supplant clinical reasoning. The levels of evidence are

Abbreviations: AKI, acute kidney injury; AL, amyloidosis; ASCT, autologous stem cell transplantation; EBV, Epstein–Barr virus; IMWG, International Myeloma Working Group; LCDD, light-chain deposition disease; MGRS, monoclonal gammopathy of renal significance; MGUS, monoclonal gammopathy of undetermined significance; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; PTLD, posttransplant lymphoproliferative disorders; SMM, smoldering myeloma.

depicted below, and will be used throughout this manuscript to provide a framework for understanding the data (or lack thereof) supporting any recommendations made (Table 1).

3 | MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE

3.1 | Background

Monoclonal gammopathy of undetermined significance (MGUS) is the most frequently encountered plasma cell dyscrasia in clinical practice.[2] MGUS is defined as the presence of a serum monoclonal protein <3.0 g/dL, <10% clonal plasma cells in the bone marrow, and the absence of end-organ damage related to the disorder. The diagnostic criteria for plasma cell disorders is depicted in Table 2.[2] In a large study, the prevalence of MGUS was estimated at 3.2%, in a predominantly white population.[3] The most important risk of MGUS is progression to MM. A long-term study of MGUS patients, showed a cumulative probability of progression to symptomatic multiple myeloma of 12% at 10 years, 25% at 20 years, and 30% at 25 years.[4]

3.2 | Management of MGUS

The International Myeloma Working Group (IMWG) has published guidelines for the assessment of risk of progression in MGUS in the general population (Table 3), by analyzing the combination of serum monoclonal protein level, serum free light chain levels, and immunoglobulin isotype.[5] The risk classification system forms a basis for recommendations regarding management and prognosis of MGUS in the general population, which are extrapolated to the organ transplantation patient population (Tables 3 and 4). Following the diagnosis of an MGUS, and after careful evaluation for other types of plasma cell disorders, patients should be followed as per the European Myeloma Network guidelines[6] (Table 4).

3.3 | MGUS in solid organ transplant

In large study of 1016 kidney transplant patients, only 16 of 1016 (1.6%) patients had an MGUS at any time; 5 of 16 were diagnosed pre–kidney transplant, and 11 of 16 were diagnosed post–kidney transplant.[7] In a retrospective analysis of the Healthcare Cost and Utilization Project in California, only 72 of 22 062 organ-transplant patients had a known MGUS prior to OT (0.3%).[8] Another large retrospective analysis of 1593 organ-transplant patients revealed a monoclonal spike in 2.8% of patients.[9] Some degree of selection bias may be present in these results—as many transplant centers will not list or transplant patients with MGUS. This may explain the lower incidence described in these studies, as compared with the incidence in the general population described previously.

Given the inherent risks of progression to MM and the long-term immunosuppression that organ-transplant patients need—there is concern for increased risk for development of MM or other plasma cell disorders in patients with MGUS who undergo organ transplant. Immunosuppression following organ transplant can result in higher incidence of developing malignancy—approximately three to five times the general population, with non-melanoma skin cancer and non-Hodgkin lymphoma being the most common secondary malignancies.[10]

To answer this clinical concern, there are many retrospective series examining the impact of MGUS in the pre–organ transplant setting, and also in post–organ transplant patients. The data from each of these settings are summarized as follows.

3.4 | MGUS and all organ transplantation data

A large, retrospective analysis of the California Healthcare Cost and Utilization Project database evaluated patients with MGUS who underwent organ transplant between 2005 and 2011.[8] Analysis revealed that of 22 062 patients who underwent organ transplant, 72 had an MGUS prior to transplant. Of the MGUS patients, there were 10 cases of multiple myeloma after organ transplant, compared with 37 in the patients without MGUS. In another study, records of 1199 patients who underwent organ transplant (including kidney, liver, and pancreatic transplant) were reviewed.[9] A monoclonal protein was present in 2.8% of all patients. Interestingly, in liver transplant patients, 5.9% (22 of 368) had MGUS at baseline, while only 1.7% (14 of 823) of renal transplant recipients had MGUS at baseline. Of the patients who had MGUS, no progression to multiple myeloma, amyloidosis, or lymphoma was observed during immunosuppression post OT, and there was no association of MGUS with posttransplant lymphoproliferative disorder (PTLD).

3.5 | MGUS and kidney transplantation

Several small retrospective studies have examined the impact of MGUS (both in the pre– and post–organ transplant setting) on outcomes in persons undergoing kidney transplant. The largest study looked at 3518 kidney transplant patients between 1963 through 2006, and evaluated long-term outcomes in persons with an MGUS, or who develop one afterward.[11] Of the 3518 patients, 42 (1.2%) had a monoclonal protein. Only 23 of 42 had MGUS prior to transplant, and 19 of 42 had MGUS posttransplant. Progression to smoldering MM occurred in 2 (8.7%) patients, but no patient was documented to progress to symptomatic MM.

Another large retrospective study did not disclose any risk of myeloma or other plasma cell disorder in persons undergoing kidney transplant. In a study of 1016 patients who underwent KT from 1992-2012, only 16 (1.6%) were diagnosed with MGUS.[7] Five of these 16 patients were diagnosed prior to kidney transplant, and 11 were diagnosed afterward. None of the 16 patients developed MM; however, there were 2 patients (12.5%) that developed a hematologic malignancy.

In an analysis of 1215 kidney transplant candidates at a large referral center, conducted between the years of 2000 through 2007, only 34 (2.8%) were found to have an MGUS during the evaluation prior to potential kidney transplant.[12] Of this cohort,

TABLE 1 Oxford Centre for Evidence-Based Medicine 2011 levels of evidence[1]

Question	Level 1	Level 2	Level 3	Level 4	Level 5
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances	Local non-random sample	Case-series	n/a
Prognosis	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial	Case-series or case-control studies, or poor quality prognostic cohort study	n/a
Diagnosis	Systemic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards	Case-control studies, or poor or non-independent reference standard	Mechanism-based reasoning
Treatment benefits	Systemic review of randomized trials or n of 1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study	Case-series, case-control, or historically controlled studies	Mechanism-based reasoning
Treatment harms	Systemic review of randomized trials, systemic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm	Case-series, case-control, or historically controlled studies	Mechanism-based reasoning
Screening	Systemic review of randomized trials	Randomized trial	Non-randomized controlled cohort/follow-up study	Case-series, case-control, or historically controlled studies	Mechanism-based reasoning

TABLE 2 Diagnosis of plasma cell diseases and common management options

Diagnosis	Definition	Common management options
Multiple Myeloma	Clonal plasma cell population in bone marrow ≥ 10%, or bony or extramedullary plasmacytoma (biopsy proven), in addition to one or more of the following myeloma defining events: *Myeloma Defining Events* • End organ damage attributable to the plasma cell disorder, in particular ("CRAB" criteria): o Hypercalcemia o Renal insufficiency o Anemia o Bone lesions • Biomarkers of malignancy o Clonal bone marrow plasma cell percentage ≥ 60% o Involved:uninvolved serum free light chain ratio ≥ 100 o >1 focal lesions on MRI or PET-CT study	Induction therapy followed by autologous stem cell transplantation, followed by maintenance Induction therapy followed by maintenance for transplant ineligible patients Patients uniformly relapse; treatment with alternative FDA approved drugs is standard at relapse
Smoldering multiple myeloma	Serum monoclonal protein ≥ 3 g/dL and/or 10 to 60% bone marrow clonal plasma cells Absence of end organ damage or myeloma-defining biomarkers (see above under Multiple Myeloma), or systemic amyloidosis	Observation at 3- to 6-mo intervals
Monoclonal gammopathy of undetermined significance	Serum monoclonal protein < 3 g/dL Clonal bone marrow plasma cells < 10% Absence of end organ damage or myeloma-defining biomarkers (see above under Multiple Myeloma), or systemic amyloidosis	Observation at 6- to 12-mo intervals (See table 4)
Solitary plasmacytoma	Single lesion of bone or soft tissue, biopsy-proven, with evidence of clonal plasma cells Lack of clonal bone marrow plasma cells No evidence for end organ damage attributable to the plasma cell disorder, or myeloma defining events	Involved field radiotherapy followed by Observation at 6- to 12-mo intervals
Solitary plasmacytoma with minimal marrow involvement	Single lesion of bone or soft tissue, biopsy-proven, with evidence of clonal plasma cells Clonal bone marrow plasma cells < 10% No evidence for end organ damage attributable to the plasma cell disorder, or myeloma defining events	Involved field radiotherapy followed by Observation at 6- to 12-mo intervals
Systemic AL amyloidosis	Evidence for a clonal plasma cell dyscrasia (evidence of a serum or urine monoclonal protein, abnormal free light-chain ratio, or clonal bone marrow plasmacytosis) Biopsy-proven evidence for amyloidosis, as demonstrated by positive staining by Congo red in any tissue from an affected organ Clinical syndrome consistent with AL amyloidosis in vital organs (kidneys, heart, liver, gastrointestinal tract, nervous system)	Treatment with CyBorD (cyclophosphamide, dexamethasone, bortezomib) For select patients, autologous stem cell transplantation
Light chain deposition disease	Presence of a clonal plasma cell or B cell neoplasm, and Characteristic pathologic findings showing amorphous to granular deposition of monoclonal immunoglobulin components	Treatment as per underlying disorder, whether plasma cell neoplasm or B cell neoplasm For select patients, autologous stem cell transplantation

TABLE 3 Risk stratification for monoclonal gammopathy of undetermined significance in the general population

Risk group	Absolute risk progression at 20 y, %	Absolute risk of progression at 20 y accounting for death as a competing risk, %
Low risk (serum M protein <1.5 g/dL, IgG subtype, normal FLC ratio [0.26-1.65])	5	2
Low-intermediate risk (any 1 factor abnormal)	21	10
High-intermediate risk (any 2 factors abnormal)	37	18
High risk (all factors abnormal)	58	27

Factors: serum M protein < 1.5 g/dL, IgG subtype, normal FLC ratio [0.26-1.65]) (ref. 5).

only 9 patients with MGUS actually underwent transplant, and none of these patients developed MM or lymphoproliferative disease during follow-up. Spanish investigators reported outcomes of MGUS in patients undergoing kidney transplant.[13] In a cohort of 587 patients, from 1996 to 2011, 17 patients (2.9%) had an MGUS diagnosed either before or after transplant; 9 patients had an MGUS prior to transplant. Of the 9 patients with MGUS pretransplant, 1 patient did develop symptomatic MM, with a median follow-up of 6 years, and all patients still had a functioning allograft.

3.6 | MGUS in heart transplantation

In 2001, one study was published examining outcomes of MGUS patients undergoing heart transplant. This publication looked at risk factors for MGUS in a heart transplant population of 308 patients from a single center.[14] In this population, MGUS was common (76 patients, or 25%), but importantly, no patients with MGUS developed MM.

3.7 | MGUS and other organ-transplant populations

Two separate studies have examined the impact of MGUS on outcomes in patients undergoing liver transplant. The first study was a prospective analysis of 911 patients who underwent transplant.[15] Of 911 patients, MGUS was present in 114 (12.5%). Eighteen of the 114 MGUS patients developed PTLD (no diagnoses were MM), whereas only 3 patients without an MGUS developed PTLD. In a multivariate analysis, MGUS was retained as a risk factor for PTLD (relative risk [RR] of 65.3). A second study of liver transplant patients also investigated the association between MGUS and EBV-induced PTLD, in a retrospective analysis of 201 patients.[16] In a univariate analysis, development of an IgM serum monoclonal protein, or urinary monoclonal protein of any type, were associated with development of PTLD.

Beyond the liver-transplant population, there are few data focusing on specific less common transplants such as lung or pancreas. Further research is needed in these populations to define the impact of an MGUS diagnosis on long-term outcomes and risk of developing subsequent malignancy.

TABLE 4 MGUS Management Guidelines for the General Population (adapted from most recent European Myeloma Network guidelines)

Risk group[a] + life expectancy	Follow up
Low-risk MGUS, life expectancy ≥ 5 y	6 mo; if stable, every 1-2 y
Non-low risk MGUS, and life expectancy ≥5 y	6 mo, annually thereafter
MGUS and life expectancy ≤5 y	No further follow-up[b] indicated; additional investigations only if symptoms would warrant

[a]Risk of progression as predicted by the Mayo Clinic risk stratification model (Table 2).
[b]Follow-up generally includes periodic assessment with SPEP, serum free light chains, CBC and basic metabolic panel.

3.8 | MGUS and living donors

During the last decade, living kidney donor transplantation has increased in numbers, and given the long wait lists for deceased donor kidney transplants, may be the only practical option for some patients.[17,18] The Amsterdam Criteria for living kidney donors, published in 2005, specifically advises against the use of donors with a monoclonal gammopathy.[19] Since then, there have been concerning reports in the literature regarding the impact of MGUS in a living donor kidney transplant. In a report of 2 cases wherein the donor had an MGUS, neither of the 2 recipients developed multiple myeloma nor any complications.[20] However, another report of 2 organ donors, and 7 organ recipients, described transmission of PTLD to all 7 recipients (2 cases of lymphoplasmacytic lymphoma, 2 MGUS, 3 cases of MM).[21] The origin of malignancy (ie, donor derived) was confirmed using microsatellite analysis. There have been 2 other case reports of myeloma of donor origin arising after kidney transplant.[22,23] At this time, further study is needed with large registry-based analyses to determine the cause and effect relationship of donor MGUS and PTLD in recipients.

3.9 | MGUS recommendations

1. Based on the current data, we do not recommend routinely testing organ transplant recipients for MGUS, either in the pre- and posttransplant settings (Level 4).
2. Based on limited, nonrandomized retrospective evidence, we do not think that a diagnosis of MGUS in a recipient should preclude organ transplantation (Level 3).

3. If a potential organ transplant recipient is known to have MGUS, then further testing (Table 2) is needed to evaluate for an active plasma cell disease, based on current guidelines (Tables 3 and 4).

4 | MULTIPLE MYELOMA

4.1 | Background

Multiple myeloma (MM) is the most common plasma cell neoplasm, classically characterized by the "CRAB" criteria (hypercalcemia, renal failure, anemia, bone lesions). Currently MM is considered an incurable cancer, but survival for multiple myeloma has been improving with better therapies. From 1975 to 1977, the 5-year survival rate was only 25%, whereas more recently, from 2005 to 2011, the 5-year survival rate has improved to 49%.[24] It is important to note that the diagnosis of MM no longer imparts a poor and rapidly lethal prognosis for patients. The disease is now highly treatable in the majority of patients. In fact, the survival of MM patients is now similar to that of otherwise similar patients without MM.[25]

The diagnosis of MM is made with the presence of ≥10% clonal bone marrow plasma cells, or presence of a biopsy-proven bony or extramedullary plasmacytoma, with one or more myeloma-defining events (Table 1).[26] Myeloma-defining events include both evidence of end-organ disease, and biomarkers of malignancy (Table 2).

Therapy for newly diagnosed multiple myeloma in 2017 consists of two or three drug combinations of proteasome inhibitors, immunomodulatory drugs, and steroids.[27] Approved immunomodulatory drugs include lenalidomide, thalidomide, and pomalidomide. The mechanism of action of these drugs involves binding to cereblon, which results in activation of cereblon E3 ligase activity.[28-30] Proteasome inhibitors include bortezomib, ixazomib, and carfilzomib. Bortezomib reversibly inhibits the 20S proteasome, resulting in stress on the unfolded protein response pathway, and inhibition of NF-kappa B, leading to apoptosis.[31]

Autologous stem cell transplantation (ASCT) is a standard component of initial therapy for eligible patients, depending on age, overall health, and organ function. Although ASCT is not a curative treatment, it is a highly effective therapy for many patients that can provide meaningful, long-term remissions from myeloma. For patients who are eligible, upfront treatment with the triplet regimen VRD (bortezomib, lenalidomide, and dexamethasone), followed by consolidation with ASCT followed by long-term maintenance therapy is the preferred approach.[27] Maintenance therapy—defined as a low dose of an effective therapy after initial treatment—has been studied after autologous transplantation with lenalidomide and bortezomib, and both drugs are effective at prolonging remissions.[32,33]

For those who are transplant ineligible, upfront treatment with two or three drug combinations, followed by maintenance therapy is the standard approach. For patients with relapsed disease, many new agents are now FDA approved, including next generation proteasome inhibitors and immunomodulatory agents, monoclonal antibodies targeting CD38 (daratumumab), SLAMF7 (elotuzumab), and histone deacetylating inhibitors (HDAC inhibitors) like panobinostat.[34]

Myeloma therapy can have clinically significant acute and long-term side effects. Immunomodulatory drugs lenalidomide and pomalidomide can cause rash, cytopenias, increased risk for thromboembolism, and an increased risk for secondary malignancies.[35,36] Proteasome inhibitors such as bortezomib have a risk of neuropathy, and immune suppression leading to reactivation of shingles.[35,36] A thorough discussion of post-ASCT complications is beyond the scope of this paper, but immunocompromised state lasts well beyond engraftment, and infectious complications may occur up to a year post-ASCT.

4.2 | Kidney transplantation in multiple myeloma

Acute kidney injury (AKI) is a common end-organ complication of multiple myeloma. Up to 50% of patients with newly diagnosed MM will present with AKI secondary to multiple myeloma.[37] Although formerly associated with a poor prognosis in newly diagnosed MM, introduction of newer drugs has led to an improvement in outcomes for patients with AKI secondary to MM.[38] Despite improved outcomes, some patients still develop long-term, dialysis-dependent end-stage renal disease. Many patients with MM remain on dialysis long term, thus raising the question of the suitability of kidney transplantation in this population.

Given the continuous risk of MM relapse and thus risk to a renal allograft, there has been only limited enthusiasm from centers for kidney transplantation for MM. Data remain limited to case reports only; only recently has there been a review of the published literature.[39] Thus, without more evidence, and understandably limited enthusiasm for kidney transplant in MM patients, this should be likely only considered in the context of a prospective trial. A case can be made to study this approach, however—especially in those MM patients with the best outcomes—the revised ISS stage I patients whose 5-year survival rates approach ~80% in the US.[40]

4.3 | Screening recommendations

Kidney Transplantation for Multiple Myeloma: Given the lack of sufficient evidence, kidney transplant for MM related renal impairment should not be routinely recommended (Level 4). Further study is needed to define the optimal candidates for this procedure through prospective trials.

4.4 | Development of multiple myeloma after organ transplant

Multiple myeloma has also been studied in the post-organ transplant setting, where it can occur in the spectrum of PTLD. A diagnosis

of multiple myeloma in the post–organ transplant setting is fairly straightforward. Best classified as a monomorphic PTLD, multiple myeloma in this setting pathologically appears as sheets or clusters of infiltrative plasma cells in the marrow with a characteristic expression of surface markers.

Several publications have suggested a higher risk of multiple myeloma in transplant recipients compared to the general population—as captured by the standardized incidence ratio. A large retrospective review of the US solid organ transplant registry was conducted in 2013.[41] This study examined 202 600 recipients of organ transplants from the years 1987-2009, and documented 140 cases of plasma cell neoplasms developing post-transplant, with a standardized incidence ratio of 1.8. Of these patients, 102 were MM, and 38 were plasmacytomas, with standardized incidence ratios of 1.41, and 7.06, respectively. Epstein-Barr virus (EBV) status of tumors was available in 18 cases, of which 39% were EBV-positive, far higher than the rates in plasma cell neoplasms that develop in nonimmunosuppressed people, suggesting some importance for EBV in the development of at least some plasma cell neoplasms posttransplant. A meta-analysis of immunosuppressed patients (both from human immunodeficiency virus and organ transplant) also documented slightly elevated risks for MM in these populations, with a standardized incidence ratio of 3.12 for MM in organ-transplant patients.[42] Finally, another retrospective analysis of data from the United Kingdom Transplant Registry documented standardized incidence ratios ranging from 0.8 up to 3.3 in different transplant types.[43] Thus, there appears to be a modest elevation in risk for development of MM in the organ transplant population as compared with the general population, based on the results of these studies.

There are few data regarding specific cases of MM that have developed post–organ transplant as a PTLD. Recently, a smaller study conducted described the development of MM post–organ transplant, specifically, in kidney transplant patients.[44] They searched the medical record between the years 1994-2013 and used a combination of ICD codes and notes to identify patients who developed MM post–kidney transplant. A total of 7 patients using this search were identified. Of these patients, only 4 had an antecedent MGUS prior to transplant, and the median time from transplant to MM diagnosis was 70 months. Of note, allograft failure occurred in 4 of 7 patients due to MM related AKI.

A frequently encountered question with respect to development of MM after OT is whether modulation of immunosuppression is indicated. The impetus for this has been (1) in PTLD, modulation of immunosuppression is often utilized as a therapeutic maneuver to treat the neoplasm, and (2) therapy for MM and other plasma cell disorders is often immunosuppressive. There are little data to help guide us in this scenario, and management is mechanistic-based. Some degree of modification of the immunosuppression medications are likely necessary to mitigate excessive immunosuppression from both, although this is not strictly evidence-based. The major concern with respect to initiating anti-myeloma therapy is increased risk of infections while on immunosuppression and combination novel drug therapy for MM. There are few data to suggest that decreasing immunosuppression can lead an MM PTLD to resolve.

5 | MONOCLONAL GAMMOPATHY OF RENAL SIGNIFICANCE

5.1 | Background

Monoclonal gammopathy of renal significance (MGRS) is a term defining monoclonal gammopathies that result in kidney disease. The most common plasma cell dyscrasias a clinician will encounter that fall under the MGRS category include light chain deposition disease (LCDD), cryoglobulinemia (Type 1 and 2), and monoclonal gammopathy-associated C3 glomerulopathy.[45] Most critical for the clinician assuming care of MGRS patients is having tools to prevent further renal impairment and understanding the role of kidney transplant in this disease group. Herein, we will review some of the more common MGRS diseases, and the data supporting kidney transplant for each.

5.2 | Light chain deposition disease

5.2.1 | Background

Light chain deposition disease results from deposition of immunoglobulin light-chains along the glomerular and tubular basement membranes of the kidneys.[46] Proteinuria is a common presenting sign, with subsequent development of progressive decline in renal function and irreversible damage, often resulting in need for long-term renal replacement therapy.[46] The underlying cause for LCDD is excessive production of abnormal immunoglobulins by a clonal plasma cell dyscrasia. Treatment thus targets the underlying clonal plasma cell disease with systemic chemotherapy and novel agents. Initial studies examining ASCT in LCDD have documented successful long-term remissions (ie, long periods of time, on the order of years, without evidence for disease recurrence). An early study in 2004 described outcomes in 11 patients with LCDD undergoing ASCT.[47] No reports of ASCT related mortality were described, and 8 of 11 patients had disease response, with histologic regression documented in cardiac, liver, and skin biopsies. Another publication in 2008 showed good tolerability of ASCT and long-lasting responses.[48] Of 6 patients with LCDD who underwent ASCT, 5 survived, all of whom achieved a remission of their disease. The median reduction in proteinuria was 92%, and median improvement in GFR was 95%.

5.2.2 | Kidney transplantation in LCDD

In patients with LCDD, with effective treatment of the primary hematologic disorder with ASCT, one could consider solid organ transplant for patients with dialysis-dependent renal failure. However, this idea has had little enthusiasm, given concerns for recurrence of the plasma cell disorder and organ damage from

immunoglobulin deposition. The pertinent literature will be reviewed to follow.

The earliest publication, in 2004, was a retrospective review of 7 patients with LCDD who underwent kidney transplant.[49] In this study, renal allograft survival was noted to be significantly reduced, with a median of 33.8 months to recurrence of renal disease. A later publication in which 9 patients underwent transplant for LCDD described 3 of 9 patients who had renal progression, and 6 of 9 who had progression of the underlying plasma cell disorder, but were initiated on subsequent plasma cell directed therapy and had a response to that, without any worsening of renal disease.[46]

Another group at a large referral center reported on a large cohort of patients with LCDD who were followed there.[50] Of 53 patients with LCDD, 7 underwent kidney transplant, and for those patients with long-term remission of the plasma cell disorder, there was no evidence of recurrence of LCDD up to 9.7 years later. Accordingly, there was noted to be a strong relationship between response of the underlying disease and renal outcomes with respect to kidney transplant.

5.2.3 | Kidney transplantation in LCDD—recommendations

1. Kidney transplantation for LCDD is an attractive approach for management of end stage renal disease, however, in the absence of long term disease remission, there is ongoing risk of recurrent immunoglobulin deposition and allograft failure. Further research is needed to define the optimal candidates for this procedure, likely incorporating a sustained period of hematologic remission.
2. We recommend that for a patient with LCDD to be considered for kidney transplant, prior ASCT or chemotherapy with evidence of a hematologic remission would be required for the best chance for long-term graft survival (Level 4).

5.3 | Cryoglobulinemia

Immunoglobulins which precipitate under temperatures less than 37 degrees Centigrade are referred to as cryoglobulins. There are two common types of cryoglobulins: Type I—a single monoclonal immunoglobulin, and Type II—a monoclonal immunoglobulin and a corresponding antigen, often a rheumatoid factor. A range of different diseases may be associated with cryoglobulins, including hematologic malignancy, autoimmune diseases, or infections.[51]

When the cryoglobulinemia is associated with an underlying hematologic disease, treatment of the hematologic neoplasm is often indicated and may reverse renal dysfunction. A case series of patients with multiple myeloma and Type I cryoglobulinemia, reported on outcomes of 7 patients.[52] Of these patients, 2 developed renal failure, and had a full recovery following treatment for MM. Another larger series of patients with Type I monoclonal cryoglobulinemia reported on 102 patients.[53] Of the 102 patients, 94 had an underlying hematologic disorder—most commonly MGUS in 39, MM in 20, and lymphoplasmacytic lymphoma in 21. Seventy-three patients underwent treatment for the underlying disorder; of these patients, 47 (64%) showed symptomatic improvement in renal function with first-line therapy.

Cryoglobulinemia may also occur as a complication post kidney transplant. In a small study of 39 kidney transplant recipients, cryoprecipitate was detected in 29/39 (74.4%) of patients, of whom approximately one-third had evidence of hepatitis C viral infection.[54] Interestingly, in these patients, few had active signs or symptoms of circulating monoclonal cryoglobulins, and graft function did not appear to be impacted. However, in some cases, cryoglobulins may impact graft function, and small studies have suggested that B-cell depletion may be of benefit. A study in 7 patients posttransplant with mixed cryoglobulinemia, showed that treatment with rituximab—a monoclonal antibody directed against the CD20 antigen—could result in clinical remissions in patients.[54]

5.3.1 | Kidney transplant in cryoglobulinemia—recommendations

1. There is little data supporting the use of kidney transplant for end stage renal disease secondary to cryoglobulinemia. For those patients with an underlying plasma cell dyscrasia or lymphoid malignancy, directed therapy toward the underlying B-cell clone should be undertaken before kidney transplant is considered, as many of these patients will achieve remission with anti-neoplastic therapy (Level 4).
2. For patients who develop cryoglobulinemia post-kidney transplant, treatment of the underlying B-cell clone with agents such as rituximab or alkylators may be of benefit (Level 4).

5.4 | C3 glomerulopathy

Recently classified as an MGRS, C3 glomerulopathy (C3G) is a condition characterized by glomerular lesions with C3 complement deposition in the absence of immunoglobulin deposits.[55,56] In a recently published retrospective analysis of 50 adult patients in France with monoclonal gammopathy and biopsy-proven C3G, some benefit of treatment of the underlying plasma cell dyscrasia, with improvement in renal disease, was noted.[57] In this series, most had severe renal disease, with 42 of 49 having stage 3-4 chronic kidney disease, and 47 of 49 having monoclonal gammopathy. Twenty-nine patients received chemotherapy; of these, achievement of a hematologic response (ie, reduction or absence of the abnormal, disease-causing serum monoclonal protein by >50%) was associated with improved renal recovery. Although these are retrospective data, these findings suggest a benefit and further study is needed, to define the role of anti-plasma cell directed therapy in patients with C3G. There are no data supporting the use of kidney transplant in patients with C3G.

5.4.1 | Kidney transplant in C3 glomerulopathy—recommendations

1. Recent retrospective data suggest that in patients with C3G who have an underlying plasma cell disorder, treatment may result in improvement in renal function (Level 3). This should be considered carefully in consultation with a hematologist-oncologist in all patients with C3G who are undergoing evaluation for kidney transplant.
2. Hematologic remission of an underlying B-cell clone or plasma cell neoplasm appears to be beneficial before kidney transplant for patients with C3G to mitigate the risk of recurrence and allograft failure (Level 5). However, further controlled trials are necessary to definitively answer this question.

6 | IMMUNOGLOBULIN LIGHT-CHAIN AMYLOIDOSIS

6.1 | Background

The amyloidoses are a heterogeneous group of disorders characterized by deposition of insoluble fibrils as beta-pleated sheets, known as amyloid fibrils. The most common type of amyloidosis is primary systemic immunoglobulin light-chain (AL) amyloidosis, caused by a clonal plasma cell dyscrasia producing amyloidogenic light-chains. Typical sites of organ involvement by amyloidosis include the kidneys in 67%, gastrointestinal tract in 80%, heart in 50%, and nerve involvement in 20% of patients.[58] Left untreated, AL amyloidosis is a devastating condition, often resulting severe morbidity and mortality. The diagnostic criteria for AL are described in Table 2.

Treatment for newly diagnosed AL amyloidosis consists of combination drug regimens (primarily bortezomib-based) and ASCT. The goal is to induce remission of the clonal plasma cell dyscrasia that causes amyloid deposition. However, these treatments are not considered curative.[59] Long-term follow-up of these patients who underwent ASCT for AL amyloidosis was published in 2011. The median overall survival was 6.3 years, and 8.3 years for those patients who achieved hematologic complete responses.[60] The critical importance of the hematologic complete response in amyloidosis and all other plasma cell disorders—defined as absence of the abnormal monoclonal protein in blood and urine, and thus, no detectable evidence of disease—lies in its association with long term, durable remissions (ie, a remission characterized by a long period of time without measurable signs of cancer. The duration of time qualified for a remission to be "durable" varies by oncologist, but typically indicates a remission lasting at least 3+ years).

The most frequently used nontransplant treatment for AL amyloidosis is the combination of cyclophosphamide (an alkylator), bortezomib (a proteasome inhibitor), and dexamethasone—known as CyBorD. In an early study, responses were noted in 16 of 17 patients (94%), with a median time to response of only 2 months.[61] Furthermore, it should be noted that the quality of response of AL amyloidosis with bortezomib is outstanding, and recently a study has suggested that the outcome of these patients may be equivalent in patients who have bortezomib-based regimens only or ASCT.[62] Beyond this combination, other new drugs have changed the landscape for AL, such that with relapse of the abnormal protein in the blood, most patients can be successfully treated and achieve repeated remissions.[63-66]

Despite progress in treatments for AL amyloidosis, the disease remains devastating for many, especially those patients with advanced cardiac involvement.[67] For those patients with advanced organ failure, solid organ transplantation—heart or kidney transplantation—has been tested in small case series, often in conjunction with ASCT, though the widespread application of organ transplant has yet to achieve consensus.

6.2 | Kidney transplantation in AL amyloidosis—background

In AL amyloidosis, renal involvement is the most common site of organ involvement, occurring in approximately two-thirds of patients with amyloidosis.[68] Proteinuria is a common manifestation of renal amyloidosis, and many patients will have nephrotic-range proteinuria (up to 28%).[68] Despite effective treatment, many patients still experience renal progression culminating in a need for renal replacement therapy. In a series of 145 patients with biopsy-proven AL amyloidosis of the kidneys, 42% ultimately needed dialysis.[69]

An early study, published in 2005, first reported on outcomes of patients with AL amyloidosis with renal involvement who underwent ASCT and living donor kidney transplantation.[70] In this series, 8 patients with AL-associated end stage renal disease on dialysis underwent sequential living donor kidney transplantation, followed by mobilization and collection of autologous peripheral blood stem cells in 6 of 8, and ASCT in 5 of 8. Notably, all 6 patients who underwent ASCT had stable renal allograft function, and with a mean follow-up of 18 months, none of the patients had shown clinical or laboratory evidence of recurrent AL disease in the kidneys.

In another publication, outcomes of 19 patients with AL-associated renal disease who underwent both kidney transplant and ASCT were presented.[71] Eighteen patients underwent living donor kidney transplant, while 1 received a deceased donor transplant. There was no difference between the median graft survival and the median overall survival, and at the time of study, 79% of patients remained alive. Importantly, recurrent amyloid deposition in the kidneys occurred in only 2 of 19 patients. Although these results are promising, the small sample size limits any conclusions that should be drawn. In a subset of patients presented from a larger publication on organ transplant in AL amyloidosis, a publication reported on follow-up in patients with AL amyloidosis who underwent kidney transplant.[72] Twenty-two patients underwent transplant; 19 received deceased donor transplant, and 3 had live donors. Nineteen had received either chemotherapy or ASCT prior to transplant.

Notably, no allograft failed due to recurrent amyloid deposition; 2 grafts failed from chronic allograft nephropathy, and one related to recurrent pyelonephritis.

6.3 | Kidney transplantation in AL amyloidosis—recommendations

1. Limited data in small series of patients suggest that kidney transplantation in AL amyloidosis is feasible, with long-term allograft survival (Level 4). This has been made increasingly possible with improved treatments, including combination therapy with proteasome inhibitors, as well as high-dose therapy. In select patients with deep and lasting hematologic remissions, kidney transplant should be considered.
2. Further study is needed to definitively define the optimal patient selection criteria and sequencing of therapies prior to or following kidney transplant to optimize outcomes and reduce risk of recurrent amyloid deposition.

6.4 | Cardiac transplantation in AL amyloidosis—background

Cardiac involvement in AL amyloidosis is both common—seen in at least 50% of patients—and associated with the worst outcomes with respect to overall disease-related mortality. Those patients who present with decompensated congestive heart failure have a median survival of 6 months, with only 6% surviving for 3 years.[68,73] Unfortunately, due to decline in performance status and severity of heart failure, many of these patients are not eligible for ASCT.

As a strategy to overcome disease injury from cardiac amyloid deposition, cardiac transplantation may allow for receipt of ASCT. Sequential heart transplantation followed by ASCT has been tested in several centers. Criticism of this approach has focused on 2 critical issues. Transplant hearts remain a limited resource and should be used only in patients in whom long term survival is not expected to be limited. Second, there are concerns that amyloid will recur in the transplanted heart and other organs. Thus, the practice remains controversial and the majority of centers will still not consider patients with amyloid cardiomyopathy for heart transplant.

A first series of patients with AL amyloidosis and significant cardiac involvement who underwent sequential heart transplantation followed by ASCT was published in 2008.[67] In this series, 11 patients underwent sequential heart transplant and ASCT between 1994 and 2005. Treatment-related mortality from ASCT occurred in 2 of the 11 patients (18%). The 1- and 5-year survival from time of heart transplant was 82% and 65%, respectively. Follow-up of these data were published in 2016.[74] With a total of 23 patients who underwent sequential heart transplant and ASCT—20 of 23 had died since the procedure, with a median OS of 3.5 years for all patients. Nonetheless, patients in whom a durable (deep) hematologic response was achieved had among the best outcomes, with a median OS of 10.8 years in 7 patients with a complete response.

A joint effort from two large tertiary centers, combining heart transplant followed by ASCT at was developed.[75] Of 9 patients who underwent heart transplant, 8 underwent sequential ASCT. With a median follow-up of 56 months, 5 of 7 were still alive without recurrence of amyloidosis at the time of publication. Another study, also reported on outcomes with patients with AL amyloidosis undergoing cardiac transplantation.[72] Of 14 patients who underwent transplant, the median OS was 7.5 years; 2 perioperative deaths occurred. Amyloid recurrence was documented to have occurred in 5 allografts. Finally, another effort from Europe published a series of 8 patients with AL amyloidosis and cardiac involvement who underwent heart transplant.[76] Of these patients, 6 had received oral melphalan and dexamethasone, and 1 had previously undergone ASCT. Three patients underwent sequential heart transplant and ASCT. After a median follow-up of 26 months, 6 were still alive, and 4 patients had a sustained complete response of the underlying disease.

6.5 | Cardiac transplantation in AL amyloidosis—recommendations

1. Further study is warranted to improve outcomes for cardiac transplantation in patients with AL amyloidosis and cardiac involvement. Although promising results have been described in small series, this approach needs further study in larger clinical trials (Level 3).
2. The available data lead us to conclude that heart transplant for patients with AL amyloidosis cannot be routinely recommended (Level 3).

7 | FUTURE DIRECTIONS

We have attempted to compile and summarize the body of knowledge regarding the management of plasma cell diseases in the organ transplant setting. However, in several arenas, further research is needed. Although the data we summarize suggests no increased risk for MGUS patients undergoing organ transplant, there remain lingering concerns regarding the safety of live donors with an MGUS. Real concerns exist among the transplant community regarding the suitability of performing organ transplantation for patients with organ failure due to an underlying plasma cell disease; however, with improved novel-agent therapies, and newly-approved monoclonal-antibody based therapies, survival and outcomes will continue to improve for many patients with these diseases. It is plausible that in the near future, there will be a tipping point—at which point survival gains due to improved treatments for plasma cell diseases may allow successful organ transplant without putting the allografts at risk for recurrent monoclonal protein induced organ damage.

8 | CONCLUSION

Since its inception, solid organ transplantation has emerged as an effective and relatively safe intervention to overcome organ

failure. Herein, we have reviewed the various plasma cell disorders which may often exist as a prior diagnosis of little consequence—with the primary example of MGUS in organ transplant—or are a major underlying contributor to organ failure. Attempts at organ transplant may be fraught with risk of allograft failure from recurrence of complications of the plasma cell disease. As we have seen with multiple myeloma and AL amyloidosis—organ transplantation is feasible, but risk of disease recrudescence and allograft failure is ever-present, even in those patients with a sustained deep hematologic remission.

Despite these shortcomings, there has been striking progress in treatment of plasma cell disorders. Recently, proteasome inhibitors and immunomodulatory agents in combination with traditional high-dose chemotherapy have dramatically improved outcomes for many patients. Newer promising agents, such as CD38 monoclonal antibodies have the promise to build upon what has already been a dramatic improvement in survival. As such, organ transplant should play an increasingly prominent role in the management of organ failure related to an underlying plasma cell disorder. With better therapies resulting in longer durations of remission for more patients, organ transplantation may open to many more patients in the future.

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

REFERENCES

1. OCEBM Levels of Evidence Working Group. *The Oxford Levels of Evidence 2*. Oxford Centre for Evidence-Based Medicine. https://www.cebm.net/index.aspx?o=5653
2. Kyle RA, Rajkumar SV. Management of monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM). *Oncology (Williston Park)*. 2011;25(7):578-586.
3. Kyle RA, Therneau TM, Rajkumar SV, et al. Prevalence of monoclonal gammopathy of undetermined significance. *N Engl J Med*. 2006;354(13):1362-1369.
4. Kyle RA, Therneau TM, Rajkumar SV, et al. A long-term study of prognosis in monoclonal gammopathy of undetermined significance. *N Engl J Med*. 2002;346(8):564-569.
5. Rajkumar SV, Kyle RA, Therneau TM, et al. Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance. *Blood*. 2005;106(3):812-817.
6. van de Donk NW, Palumbo A, Johnsen HE, et al. The clinical relevance and management of monoclonal gammopathy of undetermined significance and related disorders: recommendations from the European myeloma network. *Haematologica*. 2014;99(6):984-996.
7. Cuellar-Garcia C, Sevillano Ruiz-Mateos C, Mazuecos Blanca MA, et al. Follow-up monoclonal gammopathy of undetermined significance in kidney transplant. *Transpl Proc*. 2015;47(1):78-80.
8. Goebel TE, Schiltz NK, Woodside KJ, et al. Neoplastic and non-neoplastic complications of solid organ transplantation in patients with preexisting monoclonal gammopathy of undetermined significance. *Clin Transplant*. 2015;29(9):851-857.
9. Jimenez-Zepeda VH, Heilman RL, Engel RA, et al. Monoclonal gammopathy of undetermined significance does not affect outcomes in patients undergoing solid organ transplants. *Transplantation*. 2011;92(5):570-574.
10. Chapman JR, Webster AC, Wong G. Cancer in the transplant recipient. *Cold Spring Harb Perspect Med*. 2013;3(7):a015677.
11. Naina HV, Harris S, Dispenzieri A, et al. Long-term follow-up of patients with monoclonal gammopathy of undetermined significance after kidney transplantation. *Am J Nephrol*. 2012;35(4):365-371.
12. Soltero L, Carbajal H, Xu J, et al. Initial survival data of kidney transplant patients with pre-transplant monoclonal gammopathy. *Clin Transplant*. 2012;26(2):300-304.
13. Bancu I, Canas L, Juega FJ, et al. Outcomes of monoclonal gammopathy of undetermined significance in patients who underwent kidney transplantation. *Transpl Proc*. 2015;47(8):2344-2345.
14. Caforio AL, Gambino A, Belloni Fortina A, et al. Monoclonal gammopathy in heart transplantation: risk factor analysis and relevance of immunosuppressive load. *Transpl Proc*. 2001;33(1–2):1583-1584.
15. Lemoine A, Pham P, Azoulay D, et al. Detection of gammopathy by serum protein electrophoresis for predicting and managing therapy of lymphoproliferative disorder in 911 recipients of liver transplants. *Blood*. 2001;98(5):1332-1338.
16. Badley AD, Portela DF, Patel R, et al. Development of monoclonal gammopathy precedes the development of Epstein-Barr virus-induced posttransplant lymphoproliferative disorder. *Liver Transpl Surg*. 1996;2(5):375-382.
17. Ellison MD, McBride MA, Taranto SE, Delmonico FL, Kauffman HM. Living kidney donors in need of kidney transplants: a report from the organ procurement and transplantation network. *Transplantation*. 2002;74(9):1349-1351.
18. Horvat LD, Shariff SZ, Garg AX. Global trends in the rates of living kidney donation. *Kidney Int*. 2009;75(10):1088-1098.
19. Delmonico F. A report of the amsterdam forum on the care of the live kidney donor: data and medical guidelines. *Transplantation*. 2005;79(6 suppl):S53-S66.
20. Serra N, Revuelta I, Blade J, Oppenheimer F, Campistol JM. Monoclonal gammopathy of undetermined significance: a contraindication for living kidney donation? *NDT Plus*. 2011;4(4):256-257.
21. Felldin M, Ekberg J, Polanska-Tamborek D, et al. Donor monoclonal gammopathy may cause lymphoproliferative disorders in solid organ transplant recipients. *Am J Transplant*. 2016;16(9):2676-2683.
22. Grey M, Townsend N, Lappin D, et al. IgA myeloma of donor origin arising 7 years after allogeneic renal transplant. *Br J Haematol*. 2000;108(3):592-594.
23. Peri N, Kussick S, Bakthavatsalam R, Mitsumori L, Dighe M. Postrenal transplant non-EBV multiple myeloma of donor origin. *Am J Transplant*. 2006;6(2):419-422.
24. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin*. 2016;66(1):7-30.
25. Fonseca R, Abouzaid S, Bonafede M, et al. Trends in overall survival and costs of multiple myeloma, 2000-2014. *Leukemia*. 2017;31(9):1915-1921.
26. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International myeloma working group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol*. 2014;15(12):e538-e548.
27. Rajkumar SV. Multiple myeloma: 2016 update on diagnosis, risk-stratification, and management. *Am J Hematol*. 2016;91(7):719-734.
28. Kumar S, Witzig TE, Rajkumar SV. Thalidomid: current role in the treatment of non-plasma cell malignancies. *J Clin Oncol*. 2004;22(12):2477-2488.
29. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood*. 2008;111(5):2516-2520.

30. Parman T, Wiley MJ, Wells PG. Free radical-mediated oxidative DNA damage in the mechanism of thalidomide teratogenicity. *Nat Med*. 1999;5(5):582-585.
31. Accardi F, Toscani D, Bolzoni M, Dalla Palma B, Aversa F, Giuliani N. Mechanism of action of bortezomib and the new proteasome inhibitors on myeloma cells and the bone microenvironment: impact on myeloma-induced alterations of bone remodeling. *Biomed Res Int*. 2015;2015:172458.
32. McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2012;366(19):1770-1781.
33. Sonneveld P, Schmidt-Wolf IG, van der Holt B, et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/GMMG-HD4 trial. *J Clin Oncol*. 2012;30(24):2946-2955.
34. Casserly LF, Fadia A, Sanchorawala V, et al. High-dose intravenous melphalan with autologous stem cell transplantation in AL amyloidosis-associated end-stage renal disease. *Kidney Int*. 2003;63(3):1051-1057.
35. Botta C, Ciliberto D, Rossi M, et al. Network meta-analysis of randomized trials in multiple myeloma: efficacy and safety in relapsed/refractory patients. *Blood Adv*. 2017;1(7):455-466.
36. Qiao SK, Guo XN, Ren JH, Ren HY. Efficacy and safety of lenalidomide in the treatment of multiple myeloma: a systematic review and meta-analysis of randomized controlled trials. *Chin Med J*. 2015;128(9):1215-1222.
37. Dimopoulos MA, Sonneveld P, Leung N, et al. International myeloma working group recommendations for the diagnosis and management of myeloma-related renal impairment. *J Clin Oncol*. 2016;34(13):1544-1557.
38. Dimopoulos MA, Delimpasi S, Katodritou E, et al. Significant improvement in the survival of patients with multiple myeloma presenting with severe renal impairment after the introduction of novel agents. *Ann Oncol*. 2014;25(1):195-200.
39. Nayak L, Lazarus HM. Renal allografts in plasma cell myeloma hematopoietic cell graft recipients: on the verge of an explosion? *Bone Marrow Transplant*. 2013;48(3):338-345.
40. Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised international staging system for multiple myeloma: a report from international myeloma working group. *J Clin Oncol*. 2015;33(26):2863-2869.
41. Engels EA, Clarke CA, Pfeiffer RM, et al. Plasma cell neoplasms in US solid organ transplant recipients. *Am J Transplant*. 2013;13(6):1523-1532.
42. Grulich AE, Van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet (London, England)*. 2007;370(9581):59-67.
43. Collett D, Mumford L, Banner NR, Neuberger J, Watson C. Comparison of the incidence of malignancy in recipients of different types of organ: a UK Registry audit. *Am J Transplant*. 2010;10(8):1889-1896.
44. Safadi S, Dispenzieri A, Amer H, et al. Multiple myeloma after kidney transplantation. *Clin Transplant*. 2015;29(1):76-84.
45. Fermand JP, Bridoux F, Kyle RA, et al. How I treat monoclonal gammopathy of renal significance (MGRS). *Blood*. 2013;122(22):3583-3590.
46. Kourelis TV, Nasr SH, Dispenzieri A, et al. Outcomes of patients with renal monoclonal immunoglobulin deposition disease. *Am J Hematol*. 2016;91(11):1123-1128.
47. Royer B, Arnulf B, Martinez F, Roy L, Flageul B, Etienne I, et al. High dose chemotherapy in light chain or light and heavy chain deposition disease. *Kidney Int*. 2004;65(2):642-648.
48. Lorenz EC, Gertz MA, Fervenza FC, et al. Long-term outcome of autologous stem cell transplantation in light chain deposition disease. *Nephrol Dial Transplant*. 2008;23(6):2052-2057.
49. Leung N, Lager DJ, Gertz MA, Wilson K, Kanakiriya S, Fervenza FC. Long-term outcome of renal transplantation in light-chain deposition disease. *Am J Kidney Dis*. 2004;43(1):147-153.
50. Sayed RH, Wechalekar AD, Gilbertson JA, et al. Natural history and outcome of light chain deposition disease. *Blood*. 2015;126(26):2805-2810.
51. Trejo O, Ramos-Casals M, Garcia-Carrasco M, et al. Cryoglobulinemia: study of etiologic factors and clinical and immunologic features in 443 patients from a single center. *Medicine*. 2001;80(4):252-262.
52. Payet J, Livartowski J, Kavian N, et al. Type I cryoglobulinemia in multiple myeloma, a rare entity: analysis of clinical and biological characteristics of seven cases and review of the literature. *Leuk Lymphoma*. 2013;54(4):767-777.
53. Sidana S, Rajkumar SV, Dispenzieri A, et al. Clinical presentation and outcomes of patients with type 1 monoclonal cryoglobulinemia. *Am J Hematol*. 2017;92(7):668-673.
54. Sens YA, Malafronte P, Souza JF, et al. Cryoglobulinemia in kidney transplant recipients. *Transpl Proc*. 2005;37(10):4273-4275.
55. Fakhouri F, Fremeaux-Bacchi V, Noel LH, Cook HT, Pickering MC. C3 glomerulopathy: a new classification. *Nat Rev Nephrol*. 2010;6(8):494-499.
56. Servais A, Fremeaux-Bacchi V, Lequintrec M, et al. Primary glomerulonephritis with isolated C3 deposits: a new entity which shares common genetic risk factors with haemolytic uraemic syndrome. *J Med Genet*. 2007;44(3):193-199.
57. Chauvet S, Fremeaux-Bacchi V, Petitprez F, et al. Treatment of B-cell disorder improves renal outcome of patients with monoclonal gammopathy-associated C3 glomerulopathy. *Blood*. 2017;129(11):1437-1447.
58. Desport E, Bridoux F, Sirac C, et al. Al amyloidosis. *Orphanet J Rare Dis*. 2012;7:54.
59. Comenzo RL. How I treat amyloidosis. *Blood*. 2009;114(15):3147-3157.
60. Cibeira MT, Sanchorawala V, Seldin DC, et al. Outcome of AL amyloidosis after high-dose melphalan and autologous stem cell transplantation: long-term results in a series of 421 patients. *Blood*. 2011;118(16):4346-4352.
61. Mikhael JR, Schuster SR, Jimenez-Zepeda VH, et al. Cyclophosphamide-bortezomib-dexamethasone (CyBorD) produces rapid and complete hematologic response in patients with AL amyloidosis. *Blood*. 2012;119(19):4391-4394.
62. Kiel PJ, Trueg AO, Ferguson M, Benson M, Abonour R. Disease-free survival following high dose or standard dose therapy in patients with amyloidosis. *Br J Haematol*. 2016;174(1):153-155.
63. Kaufman GP, Schrier SL, Lafayette RA, Arai S, Witteles RM, Liedtke M. Daratumumab yields rapid and deep hematologic responses in patients with heavily pretreated AL amyloidosis. *Blood*. 2017;130(7):900-902.
64. Palladini G, Milani P, Foli A, et al. A phase 2 trial of pomalidomide and dexamethasone rescue treatment in patients with AL amyloidosis. *Blood*. 2017;129(15):2120-2123.
65. Sanchorawala V, Shelton AC, Lo S, Varga C, Sloan JM, Seldin DC. Pomalidomide and dexamethasone in the treatment of AL amyloidosis: results of a phase 1 and 2 trial. *Blood*. 2016;128(8):1059-1062.
66. Sanchorawala V, Wright DG, Rosenzweig M, et al. Lenalidomide and dexamethasone in the treatment of AL amyloidosis: results of a phase 2 trial. *Blood*. 2007;109(2):492-496.
67. Lacy MQ, Dispenzieri A, Hayman SR, et al. Autologous stem cell transplant after heart transplant for light chain (Al) amyloid cardiomyopathy. *J Heart Lung Transplant*. 2008;27(8):823-829.
68. Kyle RA, Gertz MA. Primary systemic amyloidosis: clinical and laboratory features in 474 cases. *Semin Hematol*. 1995;32(1):45-59.

69. Gertz MA, Leung N, Lacy MQ, et al. Clinical outcome of immunoglobulin light chain amyloidosis affecting the kidney. *Nephrol Dial Transplant*. 2009;24(10):3132-3137.
70. Leung N, Griffin MD, Dispenzieri A, et al. Living donor kidney and autologous stem cell transplantation for primary systemic amyloidosis (AL) with predominant renal involvement. *Am J Transplant*. 2005;5(7):1660-1670.
71. Herrmann SM, Gertz MA, Stegall MD, et al. Long-term outcomes of patients with light chain amyloidosis (AL) after renal transplantation with or without stem cell transplantation. *Nephrol Dial Transplant*. 2011;26(6):2032-2036.
72. Sattianayagam PT, Gibbs SD, Pinney JH, et al. Solid organ transplantation in AL amyloidosis. *Am J Transplant*. 2010;10(9):2124-2131.
73. Grogan M, Dispenzieri A. Natural history and therapy of AL cardiac amyloidosis. *Heart Fail Rev*. 2015;20(2):155-162.
74. Grogan M, Gertz M, McCurdy A, et al. Long term outcomes of cardiac transplant for immunoglobulin light chain amyloidosis: the Mayo Clinic experience. *World J Transplant*. 2016;6(2):380-388.
75. Dey BR, Chung SS, Spitzer TR, et al. Cardiac transplantation followed by dose-intensive melphalan and autologous stem-cell transplantation for light chain amyloidosis and heart failure. *Transplantation*. 2010;90(8):905-911.
76. Mignot A, Varnous S, Redonnet M, et al. Heart transplantation in systemic (AL) amyloidosis: a retrospective study of eight French patients. *Arch Cardiovasc Dis*. 2008;101(9):523-532.

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