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Kidney Transplantation and Monoclonal Gammopathy of Undetermined Significance

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Abstract. Plasma cell disorders are one of the most common hematologic malignancies. Monoclonal gammopathy of undetermined significance (MGUS) is defined by a serum monoclonal protein <3 g/dL, bone marrow plasma cell infiltration <10%, and most importantly absence of end-organ damage. The prevalence of MGUS in general population is estimated to be 1%–4% and its frequency increases with age with 3% among people above 50 y of age. The risk of progression to clinically significant plasma cell dyscrasia is estimated to be 1% per year. With aging population and increasing use of transplantation for the management of kidney disease in older adults, MGUS is being identified during the evaluation for kidney transplant candidacy or during the postkidney transplant follow-up. MGUS in patients with end-stage renal disease (ESRD) undergoing evaluation for kidney transplant can pose a complex management dilemma. In this article, we review the current state of knowledge about the prevalence of MGUS in ESRD population and the impact of kidney transplantation on the progression of MGUS to clinically significant plasma cell disorder. We make recommendations for the screening of ESRD patients undergoing kidney transplant evaluation and the management of MGUS after renal transplant.

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INTRODUCTION

Monoclonal gammopathy of undetermined significance (MGUS) is the most common plasma cell dyscrasia with an estimated prevalence in the general population of 1%–4% and increasing frequency with age, 3% among people above the age of 50.[1] The kidneys are frequently affected by plasma cell disorders, which are the second most common group of hematologic malignancies. In clinically significant disorders, the renal involvement has variable presentations including myeloma cast nephropathy, light chain deposition disease, immunoglobulin light chain (AL) amyloidosis, proximal tubular dysfunction, and monoclonal gammopathy of renal significance (MGRS).[2] MGUS is defined by a serum monoclonal (M) protein <3 g/dL, bone marrow plasma cell infiltration <10%, and absence of any end-organ damage attributable to monoclonal protein is considered a premalignant condition.[3] MGUS is a risk factor for development of clinically significant plasma cell dyscrasias such as multiple myeloma, immunoglobulin light chain amyloidosis, Waldenstrom Macroglobulinemia, and other non-Hodgkin lymphomas thereby warranting ongoing monitoring for progression. This risk of progression is estimated to be at 1% per year.[4] One of the most characteristic features of MGUS is absence of end-organ damage attributable to plasma cell dyscrasia. In clinical practice, we frequently encounter situations in which this association is not readily discernible. MGUS in patients who have undergone renal transplantation or are being considered for one represents one such scenario. Common questions that arise in the evaluation of such patients include what role, if any, does MGUS has in the natural history of the renal disease? Does posttransplant immunosuppression alter the natural history of MGUS? What tools and measures do we have to follow these patients? And what is the most appropriate course of management? With aging population and increasing use of transplantation for management of kidney disease in older adults, these questions are all the more relevant. In the following, we review the current state of knowledge and make recommendations for management of these patients.

Kidney transplantation has the best outcome among all forms of renal replacement therapies for the end-stage renal disease (ESRD) patients.[5] Five-year patient survival among kidney transplant recipients is 88% as compared to 35% for patients undergoing dialysis.[6,7]

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PREVALENCE OF MGUS AMONG ESRD PATIENTS

It is difficult to estimate the true prevalence of MGUS among ESRD patients. Patients with chronic kidney disease can be diagnosed with MGUS at various time periods in the natural history of the disease: before the development of ESRD, during transplant evaluation period, or during the posttransplant follow-up. Limited data suggest a prevalence of MGUS among ESRD patients ranging from similar to general population to 3-fold higher.[8] There is no established guideline to screen all ESRD patients for MGUS. In addition, no consensus exists regarding the MGUS screening requirement for renal transplant candidates. A retrospective study reviewed the records of 675 ESRD patients above the age of 50 y who were undergoing evaluation for kidney transplantation.[9] Among these, 336 patients underwent immunofixation evaluation of the serum. In this cohort, the prevalence of MGUS among ESRD patients over the age of 50 y was 9.2%, which is approximately 3-fold higher than the general population.[4] However, in another report of 1016 patients undergoing kidney transplant evaluation, MGUS was identified in 16 patients (1.6%). It is not known whether all patients undergoing transplant evaluation were screened with serum immunofixation as only 5 of the 16 MGUS patients were identified pretransplant.[10] Based upon the limited data, it is reasonable to conclude that the prevalence of the MGUS among the ESRD patients is likely to be higher than the general population.

PROGRESSION OF MGUS TO CLINICALLY SIGNIFICANT PLASMA CELL DISORDERS AFTER KIDNEY TRANSPLANTATION

Multiple studies have attempted to define the risk of MGUS progression to a malignant entity after kidney transplantation (Table 1). In a Mayo Clinic series, 42 cases of MGUS were identified among 3518 patients who underwent kidney transplantation over >40 y.[11] Twenty-three (55%) were diagnosed pretransplant and 19 (45%) were diagnosed posttransplant. During the median follow-up of 8.5 y, 4 (17.4%) pretransplant MGUS patients progressed to hematologic malignancy—2 posttransplant lymphoproliferative disorder (PTLD) and 2 smoldering myeloma. Among the 19 patients diagnosed with MGUS posttransplant, 2 developed PTLD and none progressed to multiple myeloma.

A retrospective Spanish study of 1016 kidney transplant patients noted MGUS in 16 (1.6%) patients.[10] Only 5 patients were diagnosed pretransplant. During the follow-up of these 16 patients, MGUS remained stable in 11 patients (68%), disappeared in 3 patients (18%), and progressed to clinically significant disease in 2 patients—posttransplant lymphoproliferative disease in 1 patient after 36 mo and mucosa-associated lymphoid tissue lymphoma in the other patient after 46 mo. In their series of 755 kidney transplant patients over 16-y period, a group from Montreal performed pretransplant serum protein electrophoresis (SPEP) in 375 patients, whereas 380 patients had SPEP only after kidney transplantation.[12] Thirteen out of 375 patients were identified with MGUS before transplant with 4 of these patients progressing to either smoldering multiple myeloma or light chain deposition disease posttransplantation. Forty-three patients in their cohort were diagnosed with MGUS posttransplantation with only 2 patients progressing to either multiple myeloma or light chain deposition disease. After a median follow-up of 7.5 y, 21% of posttransplant MGUS resolved spontaneously and were thought to be potentially driven by underlying cytomegalovirus (CMV) infection. Posttransplant viral infections may play a causal role in MGUS as symptomatic CMV infection after transplantion is a reported risk factor for development of MGUS.[13] Likewise, kidney transplant recipients with MGUS tend to have higher EBV viral load when compared with kidney transplant recipients without MGUS.[14] This raises the question whether these patients are at higher risk of development of EBV-related PTLD on long-term follow-up.

A second Spanish group reported their experience of 587 kidney transplant recipients over 15 y.[15] MGUS was detected in 17 kidney transplant patients with 53% (9) diagnosed pretransplant. After a median follow-up of 6 y, 8 out of 9 patients with pretransplant MGUS remained stable and 1 progressed to multiple myeloma. None of the patients developing posttransplant MGUS had progression to malignancy. In an Italian cohort of 548 kidney transplant patients, 39 (7.1%) developed MGUS posttransplant with a median follow-up time of 7.8 y and only 1 progressed to multiple myeloma.[16]

Taken together, these studies indicate low rate of progression of MGUS to multiple myeloma and lymphoproliferative disorders after transplant and provide evidence for relative safety of renal transplant among ESRD patients with MGUS in terms of progression to MM or lymphoproliferative diseases (Table 1). Similar findings have been reported for MGUS prognosis in liver transplantation.[17]

PATIENT AND GRAFT OUTCOME OF RENAL TRANSPLANT RECIPIENTS WITH MGUS

In a Texas series, patient survival among patients who received kidney transplant after diagnosis of MGUS was similar to the ESRD patients with MGUS who remained on dialysis.[9] However, after the renal transplant, there was reduced survival among transplant recipients in this small cohort. None of the other studies have raised concern about shortened survival of renal transplant recipients with MGUS.[16,18] It is difficult to draw firm conclusion based upon these studies given small number of patients with MGUS who underwent kidney transplantation. There is a need for prospective, long-term, well-designed studies to address this question. In the meantime, it is reasonable to offer kidney transplant to patients with MGUS who have developed ESRD and this remains the common practice at high-volume transplant centers.

IMPACT OF IMMUNOSUPPRESSION AFTER KIDNEY TRANSPLANT ON PROGRESSION OF MGUS TO MYELOMA

There is a perceived risk of progression of MGUS to posttransplant myeloma defining conditions or transformation to the lymphoproliferative disorders with the use of posttransplant immunosuppression. An early study performed in Switzerland described an increased incidence in MGUS development when using quadruple induction regimen (cyclosporine A, azathioprine, prednisone, and either antithymocyte globulin or muromonab-CD3 [also known as OKT3]), noting a higher proportion of MGUS with OKT3.[19] Kidney transplant recipients with MGUS are managed with both lymphocyte depleting and nondepleting induction

TABLE 1.

Progression of MGUS to clinically significant PCD after kidney transplant

Reference	Number of patients screened	Number of patients diagnosed with MGUS, N (%)	MGUS diagnosis pretransplant, N (%)	MGUS diagnosis posttransplant, N (%)	Follow-up period, y	Progression to clinically significant PCD
Naina et al[11]	3518	42 (1.2)	23 (54.8) 4 (17.5) progressed to CS-PCD	19 (45.2) 2 (10.5) progressed to CS-PCD	8.5	4 PTLD 2 smoldering myeloma
Cuellar-Garcia et al[10]	1016	16 (1.6)	5 (31.2) 1(20) progressed to CS-PCD	11 (68.8) 1(9.1) progressed to CS-PCD	2.5	1 PTLD 1 MALT-L
Gagnon et al[12]	755	56 (7.4)	13 (23.2) 4 (30.8) progressed to CS-PCD	43 (76.8) 2 (4.7) progressed to CS-PCD	7.5	3 smoldering myeloma/multiple myeloma 3 LCDD
Bancu et al[15]	587	17 (2.9)	9 (52.9) 1 (11.1) progressed to CS-PCD	8 (47.1) None progressed to CS-PCD	6.0	1 multiple myeloma
Alfano et al[16]	548	39 (7.2)	NA	39 (100) 1 (2.6) progressed to CS-PCD	7.8	1 multiple myeloma

CS-PCD, clinically significant plasma cell disorder; LCDD, light chain deposition disease; MALT-L, mucosa-associated lymphoid tissue lymphoma; MGUS, monoclonal gammopathy of undetermined significance; NA, not applicable; PCD, plasma cell disorder; PTLD, posttransplant lymphoproliferative disorder.

agents and receive maintenance immunosuppression with calcineurin inhibitors and mycophenolate mofetil with and without steroids. There was no difference in the immunosuppression regimen among patients who progressed or remained stable.[10] A systematic study of effect of immunosuppression protocol among MGUS patients undergoing renal transplantation is warranted.

SELECTION CRITERIA FOR KIDNEY TRANSPLANT

In our opinion, candidates for renal transplant with a history of plasma cell disorder, age > 50 y, or unexplained nephrotic range proteinuria during the course of kidney disease should be screened for MGUS during transplant evaluation (Figure 1). There are no consensus guidelines for MGUS screening in people >50 y of age in general population; however, in our opinion screening for kidney transplant candidates >50 y should be considered for the following reasons: based upon limited data, the prevalence of MGUS among ESRD patients over the age 50 y who were undergoing transplant evaluation is up to 9.2%, which is approximately 3-fold higher than the general population.[4,9] In addition, it is extremely important to differentiate between previously undiagnosed MGUS and MGRS during the transplant evaluation process. Screening tests should include serum protein electrophoresis with immunofixation coupled with serum-free light chains for optimal sensitivity.[20] Among ESRD patients, free light chain levels are frequently increased due to delay in clearance and the cutoff limit for the abnormal free light chain ratio has not been validated in ESRD patients. Further studies are needed to determine the clinically significant abnormal free light chain ratio. Newer technologies have been developed utilizing mass spectrometry to identify, isotype, and quantify monoclonal protein by analyzing serum samples. These advancements have the ability to detect monoclonal protein in 50%–66% of patients who previously tested negative by the use of standard methods.[21] Recently, the international myeloma work group mass spectrometry committee endorsed the use of intact MALDI-TOF method as an alternative to immunofixation in clinical practice.[22] However, further studies are needed to assess the utility of mass spectrometry in ESRD patients.

MONOCLONAL GAMMOPATHY OF RENAL SIGNIFICANCE

MGRS is diagnosed by demonstrating the monoclonal deposits by immunofluorescence on renal biopsy in a patient who would otherwise be diagnosed as MGUS.[23] At times, it is difficult to ascertain, during the transplant evaluation process, whether monoclonal gammopathy contributed to the development of ESRD or MGUS was an incidental finding. This is due to the fact that majority of the patients do not have prior renal biopsy, and many patients are diagnosed with MGUS during the transplant evaluation process. This poses a diagnostic dilemma since failure to diagnose and treat MGRS before the transplant can lead to development of recurrence in the renal allograft. These challenges were highlighted by a Mayo Clinic series detailing that 6 out of the 29 patients with recurrent membranoproliferative glomerulonephritis after kidney transplantation had circulating monoclonal proteins.[24] Similarly, recurrent light chain proximal tubulopathy has been reported in a kidney transplant recipient with MGUS. Retrospective review of the native kidney biopsy in this patient confirmed the presence of light chain-induced tubular changes in native kidney.[25] These observations call for a close collaboration between hematology and transplant nephrology teams to undertake appropriate workup of MGUS including review of the original kidney biopsy if available and bone marrow examination to identify patients whose primary cause of renal failure is monoclonal gammopathy.

FOLLOW-UP OF MGUS AFTER RENAL TRANSPLANT

It is recommended that patients undergo regular surveillance for transformation of MGUS to multiple myeloma or lymphoproliferative disorder after kidney transplant. The frequency of follow-up should be determined by the risk of transformation but at a minimum should include a serum protein electrophoresis and free light chains every 12 mo to monitor changes in M protein.[26] Based upon analysis of Mayo Clinic cohort, hematologic findings associated with high risk of transformation include an M protein ≥1.5 g/dL, non-IgM paraprotein, and abnormal free light chain ratio.[27] MGUS patients with 2 of these risk factors showed a transformation

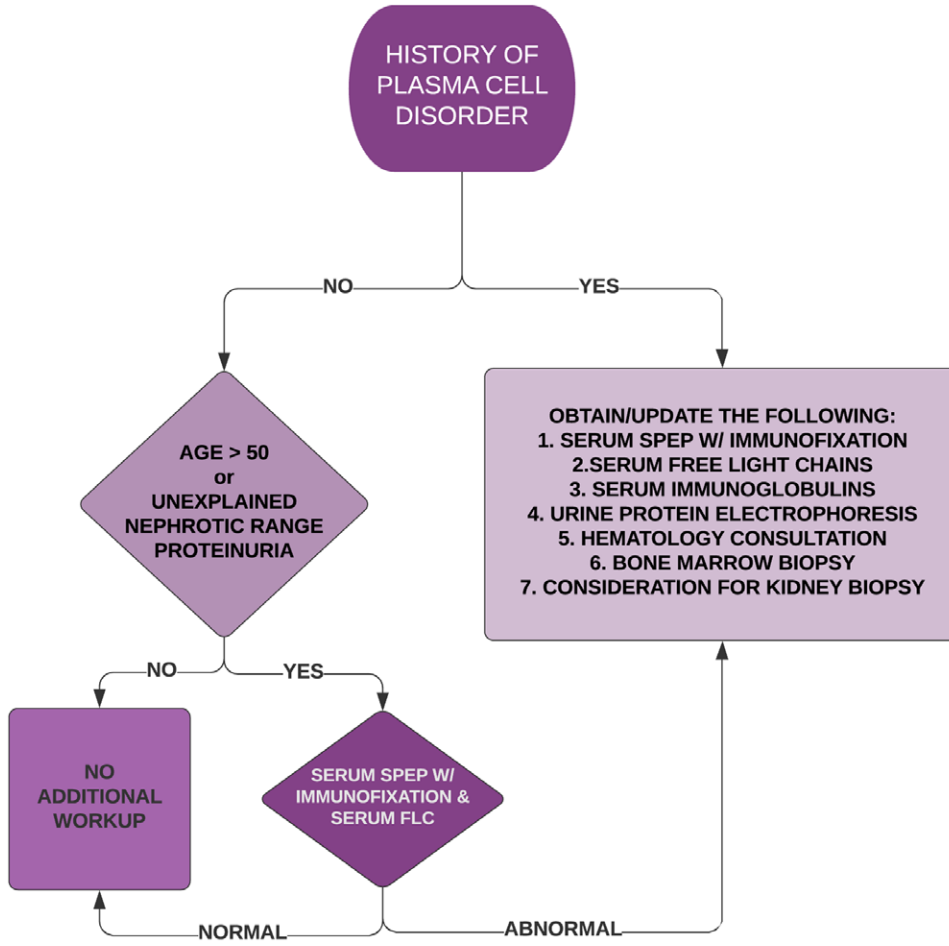

FIGURE 1. Recommended algorithm for the pretransplant evaluation. FLC, free light chain; SPEP, serum protein electrophoresis.

rate of 30% in 20 y, those with 1 risk factor had a progression rate of 20% within 20 y, and those with no risk factors showed a progression rate 7% in 20 y.[27] Based upon these findings, the international myeloma workgroup recommends whole-body imaging only in MGUS patients with high-risk characteristics.[28] In another study of 685 MGUS patients, risk factors associated with progressive MGUS were IgA isotype, M protein ≥1.5 g/dL, abnormal free light chains ratio, and ≥2 suppressed uninvolved immunoglobulins.[29] A close collaboration of transplant and hematology team is essential for timely diagnosis of progression of MGUS.

ORGAN DONORS WITH MGUS—CAN MGUS BE TRANSFERRED TO ORGAN RECIPIENTS?

There is an increasing trend of organ utilization from older living and deceased donors >50 y. The living donors who are otherwise candidates for organ donation may have MGUS and the question remains about the safety of these donors—both for donor future health and transmission of lymphoproliferative disorder via organ donation. A retrospective study performed at Mayo Clinic reported the outcome of 4 such donors with median follow-up of 5 y.[30] None of these donors developed multiple myeloma/lymphoproliferative disorder or progressed to ESRD during the follow-up period. In a case report of 2 kidney transplant recipients from donors with MGUS, there were no complications reported after a follow-up of 42 and 36 mo after transplantation.[31] However, a report of 7 organ recipients from 2 donors who had MGUS is alarming.[32] One donor transmitted lymphoplasmacytic lymphoma to 2 kidney recipients and MGUS to a liver transplant recipient. The second donor transmitted the multiple myeloma in 2 kidneys and 1 liver transplant recipient and monoclonal gammopathy in the heart transplant recipient. Removal of the transplanted kidneys from 3 recipients resulted in remission. The fourth kidney was not removed, and disease progression was noted. Retrospective review of the donor records showed no clinical signs of lymphoproliferative disorder; however, serum analysis showed large M spike in both donors. It is postulated that malignancy can be transmitted via lymphocyte/plasma cells in solid organ transplant from donor to the recipient. The available evidence on screening the older organ donors is inconclusive, and a prospective study is warranted to further assess this issue.

In summary, MGUS in patients with ESRD undergoing evaluation for kidney transplant can pose a complex management dilemma. We recommend MGUS screening for chronic kidney disease patients who have nephrotic range proteinuria or history of plasma cell disorders or age >50 y during the transplant candidacy evaluation (Figure 1). Although it is not a contraindication for renal transplant, the finding of monoclonal gammopathy should warrant thorough assessment of the patient. Close collaboration between hematologist and transplant nephrologist is important to make therapeutic

decisions. MGUS patients should be closely followed by hematologist posttransplantation for progression to clinically significant plasma cell dyscrasias. Additional studies with longer follow-up are needed to understand the natural history of MGUS in recipients of renal allograft. The role of screening for MGUS in organ donors is unclear and additional studies are needed to determine the pros and cons of such evaluation.

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