Monoclonal Gammopathies and Kidney Disease
Searching for Significance

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Over the past decade, there has been increasing interest in kidney diseases related to monoclonal gammopathies. These may occur in the setting of hematologic malignancy or when the underlying plasma or B cell clone does not meet criteria for cancer (multiple myeloma or systemic lymphoma, respectively). In the latter case, patients are diagnosed with monoclonal gammopathy of renal significance, which has historically been associated with poor prognoses; however, recent studies suggest improved kidney outcomes with treatment of the underlying clone (1). Increased recognition of paraprotein-associated kidney disease has led to important, but as of yet unanswered questions regarding screening patients with CKD for monoclonal gammopathy, and when present, determining whether the monoclonal Ig is causing kidney damage or is of undetermined significance (MGUS). These questions are especially relevant in older patients because the prevalence of both CKD and MGUS increase with age: an estimated 3.2% of patients ≥50 years of age, and up to 9% of patients >70 years of age in the United States have MGUS (2). Monoclonal gammopathy of renal significance, on the other hand, remains a rare entity, accounting for about 6%–10% of cases of MGUS, which suggests a total prevalence of <0.5% in the total United States population (2,3). Consequently, best practices for monoclonal protein testing in patients with CKD are not well established.

In this issue of *Clinical Journal of the American Society of Nephrology*, Burwick *et al.* (4) combined data from the Department of Veterans Affairs database, US Renal Data System, and Medicare to assess whether the presence of a monoclonal gammopathy is associated with higher risk of ESKD. They retrospectively analyzed 2,156,317 patients who had at least one outpatient serum creatinine and eGFR in a 1-year period from 2000 to 2001. Of the 21,898 patients who had undergone testing by either serum or urine protein electrophoresis (SPEP or UPEP) with immunofixation within 1 year of cohort entry, 2% (4593 patients) were classified as having a monoclonal gammopathy.

Medicare claims data and the US Renal Data System was then utilized to calculate ESKD risk up until 10 years from the beginning of the cohort, with an average follow-up time of 123.5 months (interquartile range, 77.5–128.5 months). In unadjusted analysis, test-positive patients had a higher risk of ESKD versus test-negative patients across all eGFR categories. However, after adjustment for factors associated with kidney disease progression, a U-shaped relationship was observed. A higher ESKD risk was observed in the groups of test-positive patients with initially preserved (eGFR≥60 ml/min per 1.73 m^2) kidney function and severely reduced (eGFR 15–29 ml/min per 1.73 m^2) kidney function (hazard ratio [HR], 1.67; 95% confidence interval [95% CI], 1.22 to 2.29; and HR, 1.38; 95% CI, 1.07 to 1.77, respectively), but not in test-positive patients with moderately reduced (eGFR 30–59 ml/min per 1.73 m^2) kidney function (HR, 1.09; 95% CI, 0.81 to 1.47). A subgroup analysis for the small number of patients who had available data on proteinuria or with a diagnosis of multiple myeloma yielded similar ESKD HRs. The authors conclude that testing for monoclonal gammopathy does not provide meaningful information on the risk of ESKD in most patients with reduced eGFR, and that the observed U-shaped curve prompts the need for further research to better understand the role of testing for those with preserved and severely reduced eGFR.

The details of ESKD etiology in this study are important to highlight. In test-positive patients with preserved eGFR at cohort entry, 27.6% (21 out of 76 patients) of ESKD was attributed to plasma cell dyscrasias (light chain nephropathy, amyloidosis, or multiple myeloma) versus 9% of test-positive patients with moderately reduced eGFR and 4% with severely reduced eGFR. This is substantially higher than the proportion of ESKD attributed to plasma cell dyscrasias among test-negative patients across all eGFR categories. This striking difference further complicates the interpretation of the results. Indeed, one could hypothesize that more widespread screening for monoclonal gammopathy in patients with preserved kidney function could lead to earlier diagnosis of plasma cell dyscrasias. Earlier diagnosis could have a substantial effect on kidney prognosis, particularly given the improved outcomes for patients with multiple myeloma and AL amyloidosis in the past two decades due to autologous stem cell transplantation and modern antiplasma cell chemotherapies (1,3,5). However, widespread screening for monoclonal gammopathy will clearly yield more diagnoses of MGUS than paraprotein-associated kidney disease. Thus, it remains unclear which patients with preserved kidney function would benefit most from screening.

These results should be considered in the context of other studies that have explored the role of testing for monoclonal gammopathy in patients with CKD, some of which examined higher-risk populations (such as patients with proteinuria, anemia, and hypercalcemia), but none of which have found an association between the presence of monoclonal gammopathy and kidney outcomes (6). However, no study to date has incorporated modern, standard-of-care testing for monoclonal proteins. Compared with prior studies that used either SPEP alone or SPEP and UPEP, Burwick *et al.* added sensitivity to detection of monoclonal proteins by evaluating serum and urine immunofixation in addition to SPEP and UPEP; however, it is not clear if patients were screened with either or both tests. Moreover, the serum free light chain assay, which maximizes the sensitivity of detection for monoclonal proteins in combination with serum and urine immunofixation, was not included because of the chosen time period of 2000–2001 (7,8). The effect on monoclonal protein detection is unknown given the variable performance of serum and urine tests across different forms of monoclonal gammopathies and the fluctuations in light chain concentrations as a result of GFR (9,10). Furthermore, in that study, if we consider the noted sensitivity and specificity of the algorithm in conjunction with the proportion of "unclassified tests" (1165 tests categorized as "unclassified" compared with 4593 tests categorized as "positive"), the effect on detection of an underlying monoclonal gammopathy and the subsequent association with risk of ESKD may be significant. The literature to date has also lacked data on monoclonal gammopathy characterization and levels of monoclonal protein over time, which are important for the diagnosis, prognosis, and treatment of clonal B and plasma cell disorders (7).

Burwick *et al.* also acknowledge that the indications for testing and resultant management as a result of paraprotein testing could not be ascertained. This is an important limitation because the associations between monoclonal gammopathy detection and ESKD risk in different groups may, in part, reflect provider practices rather than the contribution of the monoclonal gammopathy to the risk of ESKD. Interestingly, patients who did not have monoclonal protein testing had a significantly lower risk of ESKD compared with patients who were test-negative across all eGFR categories (HR, 0.37; 95% CI, 0.31 to 0.44; HR, 0.43; 95% CI, 0.36 to 0.52; HR, 0.64; 95% CI, 0.57 to 0.71; and HR, 0.78; 95% CI, 0.67 to 0.90). This may reflect selectivity in provider practices for testing in patients who may have unmeasured confounders that place them at higher risk for kidney disease progression.

Notwithstanding these limitations, the study by Burwick *et al.* provides further support that most patients with monoclonal gammopathy do not have a higher risk of CKD or ESKD that is attributable to the paraprotein. The challenge of incorporating these findings into clinical practice is their inability to shed light on the monoclonal gammopathy–associated risk for an individual patient. All monoclonal gammopathies are not created equal: host factors and specific physiochemical properties of monoclonal proteins confer the potential for end-organ damage (1,10,11), and no serologic assays exist to distinguish pathogenic from nonpathogenic paraproteins. Given the morbidity and mortality associated with CKD, ESKD, and plasma cell dyscrasias, it seems prudent to continue screening for monoclonal gammopathy in patients with unexplained kidney disease and/or proteinuria, particularly in older patients. Until more sophisticated testing is developed, the kidney biopsy will remain the only test that can truly determine the significance of an individual patient's monoclonal gammopathy.

Disclosures

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