EDITORIAL

Abnormal serum free light chain ratio does not always indicate monoclonal gammopathy

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The serum free light chain (FLC) assay (Freelite) is an antibody-based system that measures kappa and lambda immunoglobulin light chains that are unbound to heavy chains in serum. Freelite is a very sensitive method that allows to detect low concentrations of monoclonal FLCs. The measurement of serum FLC is useful in diagnosis, monitoring, prognosis, and assessing risk of progression of monoclonal gammopathies (MGs) where plasma cell clone produces only one type of FLC or intact immunoglobulin with a related overproduction of FLC.[1,2] In this assay, the reference range for the free kappa/lambda light chain ratio is 0.26 to 1.65.[3]

The paper by Niewmierzycka et al.[4] published in the current issue of the *Polish Archives of Internal Medicine*, focuses on the use of the FLC assay to identify MG in patients with chronic kidney disease (CKD) or proteinuria (or both). The presence of monoclonal protein in patients with these kidney disorders may have varied etiology including multiple myeloma (MM), immunoglobulin light chain amyloidosis (AL), light chain deposition disease, MGs related to other diseases (eg, systemic lupus erythematosus), and MG of an unknown origin (in patients with a kidney disorder not related to MG, eg, diabetes). The paper by Niewmierzycka et al.[4] is the first to address the prevalence of an abnormal kappa/lambda ratio in an unselected group of patients with proteinuria or CKD of an unknown origin (or both). Patients with these kidney disorders are very often referred for diagnostic workup for MG, and the FLC assay has become a standard diagnostic method in this clinical scenario.

Niewmierzycka et al.[4] reported that the percentage of an abnormal rFLC was highly prevalent (42.5%) regardless of the proteinuria level, estimated glomerular filtration rate (eGFR), or histopathological diagnosis on kidney biopsy. The authors conclude that an abnormal kappa/lambda ratio, although common, appears to be innocent and of no clinical significance. However, they also add that the ratio may help diagnose MM in patients with CKD or proteinuria (or both). They diagnosed 5 patients with MM (5.4%) and no cases with other MGs. In 5 patients with MM, the ratio exceeded 100 in 4 cases, and in 1 case, the ratio was 0.02.[4] In another study, the kappa/lambda ratio was abnormal in more than 90% of patients with MM, and in most cases, an involved:uninvolved FLC ratio was highly increased (>100).[5] In other MGs, especially monoclonal gammopathy of undetermined significance and AL, the kappa/lambda ratio is often lower than 100.[2] In 87 patients with CKD or proteinuria (or both), after the exclusion of MM patients, a median kappa/lambda ratio was 1.92 and it was abnormal in 39% of the patients. The authors did not provide data on the median kappa/lambda ratio in a group of non-MM patients with an abnormal ratio. The median value in the whole group (1.92) was much lower than 100, but we do not know whether there were patients with a ratio exceeding 50 or 100 (<0.02 or 0.01 in the case of the lambda chain, respectively). The tables included in the paper provide no information on the ranges of the kappa/lambda ratio. Probably these 39% of non-MM patients were characterized with an abnormal but relatively low ratio. We agree with the authors that any abnormal ratio value (eg, <100) does not exclude the presence of MM.[3]

The International Myeloma Working Group (IMWG) recommends the serum FLC assay in combination with serum protein electrophoresis (SPEP) and serum immunofixation to screen for MG other than AL, which requires all the serum tests as well as 24-hour urine immunofixation.[2] Immunofixation together with the serum FLC assay has a sensitivity of 93.8% and a specificity of 96.8% in patients examined for an MG.[6] The FLC analysis performed along with SPEP and immunofixation may reduce the need for urine

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protein studies in the initial diagnostic workup for most MGs.[7] The study by Niewmierzycka et al.[4] would provide more valuable information if SPEP and immunofixation had been performed together with the FLC assay. These methods are less sensitive but more specific for MM and MG. If serum kappa and lambda light chains and the kappa/lambda ratio are within the reference ranges, and the results of SPEP and immunofixation are normal, it is unlikely that the patient has an MG.[5,8] Conversely, an abnormal ratio, along with an increase in either kappa or lambda chain, supports the diagnosis of an MG and requires further diagnostic workup.

In 2014, the IMWG updated the criteria for the diagnosis of MM and other MGs.[9] A diagnosis of symptomatic MM requires the presence of clonal bone marrow (BM) plasma cells (PC) ≥10% or biopsy-proven bony or extramedullary plasmacytoma, and any of the myeloma-defining events (evidence of end-organ damage that may be attributed to the underlying PC proliferative disorder [CRAB: hypercalcemia, renal insufficiency, anemia, bone lesions], clonal BM PC ≥60%, involved:uninvolved serum FLC ratio ≥100 with involved FLC ≥100 mg/l, and >1 focal lesions on magnetic resonance imaging). In a previous definition of MM,[10] one of the required criteria was the presence of serum or urinary monoclonal protein (or both) detected by the FLC assay and immunofixation without a determined kappa/lambda ratio. In that case, the authors' claim that the IMWG does not provide any particular cut-off value for the kappa/lambda ratio that could be considered more specific or sensitive to diagnose MM is not justified. The authors do not specify when the data were collected.

We agree with the authors that an abnormal kappa/lambda ratio alone in patients with proteinuria or CKD (or both) is not enough to diagnose MM. However, along with other tests, it is essential to diagnose MM and other MGs.

A high prevalence of patients with an abnormal kappa/lambda ratio in this study was explained by a reduced eGFR and systemic stimulation of the immune system in the course of glomerular disease. The first cause is probably more important because the median kappa/lambda ratio in patients with CKD was higher than that in patients with both nephrotic and nonnephrotic proteinuria (3.07 vs 1.64 and 3.07 vs 1.48, respectively), and the percentage of patients with an abnormal rFLC in patients with CKD was higher than that in patients with proteinuria (47.6% vs 34.8%).[4] The ratio tended to increase together with an increasing CKD stage. The effect of the proteinuria level (glomerular disease) may also be shown by a higher median kappa/lambda ratio in patients with nephrotic syndrome than those with nonnephrotic proteinuria (1.64 vs 1.48). The abnormal ratio in patients with proteinuria may also be explained by a reduced eGFR. Tables 3a and 3b in the paper by Niewmierzycka et al.[4] show that apart from patients with CKD of an unknown origin (defined by authors as a reduced eGFR of less than 60 ml/min/1.73 m^2 without proteinuria), 64% of the patients with proteinuria also had an eGFR of less than 60 ml/min/1.73 m^2. The authors could have reported the kappa/lambda ratio in patients with proteinuria and reduced eGFR and those with proteinuria and an eGFR of less than 60 ml/min/1.73 m^2.

Patients with either polyclonal hypergammaglobulinemia (in infectious or inflammatory disorders) or renal impairment often have elevated kappa and lambda chains (even 30- to 40-fold); however, the kappa/lambda ratio usually remains normal or slightly increased.[2,3,5,6,11,12] As explained by the authors, a slightly increased ratio in renal insufficiency is caused by reduced physiological clearance and, therefore, a shorter physiological half-life of kappa chains.[1,13] These cases require careful interpretation and highlight the importance of considering additional clinical and laboratory parameters when interpreting FLC assay results. A study evaluating the kappa/lambda ratio in patients with dialysis-dependent renal failure found that the ratio may increase to 3.1, suggesting that the modified ratio (with higher values) should be used for detecting MG (0.37–3.1 vs 0.26–1.65) in this group of patients.[11] Another study confirmed that a slightly increased ratio up to 3.1 was observed with increased serum creatinine levels; therefore, renal reference intervals are recommended.[8] A ratio exceeding 3.1 is unlikely to be caused by renal insufficiency alone. In the case of a ratio between 1.65 and 3.1 in the context of renal insufficiency, further investigation with a 24-hour urine protein electrophoresis and urine immunofixation would help guide the interpretation of the results.

Niewmierzycka et al.[4] could have reported the percentage of patients with an abnormal ratio according to the renal reference range in the group of patients with an eGFR of less than 60 ml/min/1.73 m^2 (72% of the patients included into the study) because the median values of the kappa/lambda ratio in patients with CKD and in patients with CKD and proteinuria were within the renal reference range (3.07 vs 3.1 and 1.92 vs 3.1, respectively).

Another cause of an abnormal ratio in patients without MG is polyclonal hypergammaglobulinemia, caused by an increased synthesis of immunoglobulins and FLCs.[11] If the authors had performed SPEP in every patient, we would have known how many of them had polyclonal hypergammaglobulinemia, for instance, in the course of glomerular disease.

Despite the above limitations, the study by Niewmierzycka et al.[4] clearly shows that the prevalence of an abnormal, especially borderline, rFLC among patients with proteinuria or CKD of unknown origin (or both) is very high and its interpretation requires the inclusion of eGFR and further tests (SPEP, immunofixation) within the clinical context.

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