Clinical importance of serum free light chain analysis

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For 150 years, the presence of Bence Jones protein (immunoglobulin free light chains) in the urine has been an important diagnostic marker for multiple myeloma (MM). Indeed, it was the first cancer test and a century before any others. Over the last few years, however, interest in FLCs has undergone a renaissance. Development of serum tests for free kappa (k) and free lambda (l) light chains (sFLCs) has opened the door to new applications and increased their clinical importance. By way of comparison, the management of diabetes mellitus was hugely improved when blood replaced urine for glucose analysis.

From a physiological viewpoint, blood tests for small molecular weight proteins have clear advantages over urine tests. Serum FLCs are rapidly cleared through the renal glomeruli with a serum half-life of 2-6 hours and are then metabolised in the proximal tubules of the nephrons. Under normal circumstances, little protein escapes to the urine so concentrations have to increase many-fold before the absorption mechanisms are overwhelmed. Hence, urinalysis is a fickle witness to changing FLC production. Conversion to a serum test provides clarity in assessing disease processes that were previously hidden from view.

Serum concentrations of FLCs are dependent upon the balance between production by plasma cells (and their progenitors) and renal clearance. When there is increased polyclonal immunoglobulin production and/or renal impairment, both k and l FLC concentrations can increase 30-40 fold. However, the relative concentrations of k to l, i.e. the k/l ratio, remains unchanged. In contrast, tumors produce a monoclonal excess of only one of the light chain types, often with bone marrow suppression of the alternate light chain, so that k/l ratios become highly abnormal. Accurate measurement of k/l ratios underpins the utility of the sFLC immunoassays and provides a numerical indicator of clonality. Urine k/l ratios are not as dependable because the non-tumor light chain production is too low to pass consistently through the nephrons. In contrast, electrophoretic tests can only be used to quantify monoclonal light chain peaks because they are not sensitive enough to identify the non-tumor FLC concentrations.

Early clinical studies with sFLC tests were in patients with Bence Jones (light chain) multiple myeloma (MM). In two studies, on 270 sera taken at the time of clinical presentation, highly abnormal sFLC concentrations were found in every case. Furthermore, during chemotherapy, urine tests frequently normalised while serum tests remained abnormal, indicating their increased sensitivity for residual disease. In this patient group, urinalysis can now be replaced by sFLC tests. This is particularly helpful for frail, elderly patients because 24-hour urine samples are difficult to collect and results may be unreliable.

3-4% of patients with MM have so called nonsecretory disease. By definition, these patients have no monoclonal proteins by serum and urine electrophoretic tests. Nevertheless, in one study sFLC tests identified monoclonal proteins in 70% of 28 patients. Their sFLC concentrations are below the sensitivity of serum electrophoretic tests and below the threshold for clearance into the urine. Importantly, these patients can now be closely monitored by sFLC tests rather than repeated bone marrow biopsies or whole body scans.

Approximately 20% of all patients with MM have light chain or nonsecretory disease. Among the remaining patients, those who produce intact monoclonal immunoglobulins, FLCs are abnormal in 95% at disease presentation. Interestingly, the serum concentrations of FLCs and intact monoclonal immunoglobulins are not correlated. Monoclonal sFLCs are, therefore, independent markers of the disease process. This is of potential clinical use when the tumor produces large amounts of FLCs and small amounts of intact monoclonal immunoglobulins. Patients who are in apparent remission may still have residual disease as judged by elevated monoclonal FLCs. Using a similar argument, when these patients relapse, FLC concentrations may increase first before immunoglobulins. FLC chain “breakthrough” is thought to occur in 2-5% of patients who relapse after modern, intensive treatment.

An additional feature of FLC molecules is that, in contrast to intact immunoglobulins, they are
frequently nephrotoxic. Indeed, “myeloma kidney” presenting as acute renal failure occurs in approximately 10% of patients. Life expectancy is then reduced to only a few months. Myeloma kidney is particularly common in light chain only disease but in many patients with intact monoclonal immunoglobulins the sFLC concentrations are >1,000mg/L (50-100 times normal) and there is associated renal damage. The FLC assays now allow assessment of the pre-renal load of monoclonal light chains in all these patients.

There is early evidence that treatment should be aimed at normalising sFLC concentrations in order to prevent renal damage. Furthermore, rapid removal of nephrotoxic FLCs, using high cut off dialysers, can lead to renal recovery. This important new development, when used in combination with aggressive chemotherapy, should lead to significant increases in survival in this serious disease.

One particularly interesting aspect of sFLCs is their short half-life in the blood (k 2-4 hours: 1 3-6 hours). This is approximately 100-200 times shorter than the 21-day half-life of IgG molecules. Thus, FLC concentrations allow more rapid assessment of the effects of chemotherapy than do monoclonal IgG or IgA. For instance, the resistance of patients to particular drugs or drug combinations can be observed quickly and alternative treatments chosen. The 21-day half-life of IgG hides treatment responses whereas FLC analysis allows more accurate assessments.

An emerging role of sFLC analysis is for assessing the risk of progression in individuals with monoclonal gammopathies of undetermined significance (MGUS). It has been shown that the presence of an abnormal sFLC k/l ratio is a major independent risk factor for progression. In particular, the 40% of MGUS patients with low levels of IgG M-spike (<15g/L) and normal k/l ratios have a 21-fold lower risk of progression than patients with an M-spike of >15g/L, abnormal k/l ratios and non-IgG immunoglobulin class. It seems that the low risk patients can be reassured about their disease and may not need to be monitored on a long-term basis.

The predictive value of sFLCs at disease presentation extends to, asymptomatic myeloma, solitary plasmacytoma, AL amyloidosis, Waldenström’s macroglobulinaemia and MM. Indeed, initial sFLC concentrations are independent of serum albumin and b2-microglobulin as a risk factor for myeloma progression. This suggests that FLCs should be added into the current international staging system (ISS) for MM. Serum FLC tests are also of considerable importance in the diagnosis and monitoring of AL (primary) amyloidosis and light chain deposition disease.

The high sensitivity of sFLC immunoassays for tumor detection indicates they have a role in the initial screening for plasma cell dyscrasias. Currently, symptomatic patients are assessed using serum and urine protein electrophoretic tests. Since urine is frequently unavailable, it is logical to add sFLC analysis to current test protocols. Several studies have shown that there was little or no gain from urine tests so sFLC tests are likely to be widely adopted.

In summary, sFLC tests are assuming an important role in the detection and monitoring of monoclonal gammopathies. This new approach is bringing benefits to the multitude of patients with plasma cell dyscrasias. Their increasing clinical use is clearly apparent from the number of recent publications and their inclusion in international guidelines (AR Bradwell: Serum free light chain analysis; 5th Edition 2008).