The use of immunoglobulin light chain assays in the diagnosis of paraprotein-related kidney disease

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Kidney involvement is common in paraprotein-related diseases. A diversity of clinical presentations and histopathological features can occur secondary to tissue injury caused by precipitation or deposition of a clonal immunoglobulin, usually an immunoglobulin light chain. The paraprotein is either produced by multiple myeloma or by a clone of B-cell lineage that does not fulfill diagnostic criteria for multiple myeloma. The recent introduction of serum immunoglobulin free light chain assays, which accurately quantify both light chain isotypes to produce a ratio that indicates the presence or absence of a light chain paraprotein, is a major clinical development. However, as the interpretation of the assay can be challenging, the aim of this review is to clarify the role of serum and urinary light chain assays in the screening and diagnosis of paraprotein-related kidney disease.

Kidney International advance online publication, 8 October 2014; doi:10.1038/ki.2014.333

KEYWORDS: monoclonal gammopathy; monoclonal gammopathy of renal significance; multiple myeloma; serum free light chains

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Received 29 January 2014; revised 11 April 2014; accepted 8 May 2014

MONOCLONAL GAMMOPATHY AND PARAPROTEIN-RELATED KIDNEY DISEASE

Monoclonal gammopathy occurs as a consequence of a clonal proliferation of cells of B-cell lineage, particularly plasma cells, and it affects as many as 5% of the population by the age of 70 years.[1] The large majority of individuals with monoclonal gammopathy have monoclonal gammopathy of undetermined significance (MGUS), a condition that is characterized by the presence of a paraprotein (M protein) with $<10\%$ bone marrow plasma cells and importantly without end-organ damage. Recently, serum free light chain (FLC) immunoassays have been used to identify light chain only monoclonal gammopathy, with a reported prevalence of around 20% of all MGUS. Approximately 1%/yr of individuals with intact MGUS and 0.3%/yr with light chain MGUS develop a paraprotein-related disease.[1,2] Paraprotein-related disease refers to progressive proliferation of the clonal cell and/or the presence of tissue injury associated with the monoclonal gammopathy.

Kidney involvement in paraprotein-related diseases is very common and is associated with high morbidity and mortality. These poor outcomes occur both in patients with multiple myeloma and in patients who do not fulfill diagnostic criteria for multiple myeloma (Table 1). These latter patients no longer have MGUS, as the significance of the monoclonal gammopathy is now identified by the presence of an associated end-organ injury. The term 'monoclonal gammopathy of renal significance (MGRS)' has recently been proposed to emphasize the significance of a renal lesion that is directly attributable to a monoclonal immunoglobulin even though the diagnostic criteria for multiple myeloma are not met.[3]

As kidney disease associated with multiple myeloma and MGRS is usually caused by precipitation or deposition of light chain, the identification and quantification of a light chain producing clone are of particular importance in the diagnosis and management of paraprotein-related diseases. However, there is significant uncertainty about the best approach to this problem in clinical practice, including the use of serum and urinary assays[4] and the impact of kidney impairment on the interpretation of the available assays.[5] This review provides a potential systematic approach to this clinically challenging problem.

Table 1 | Renal disorders related to deposition or precipitation of monoclonal immunoglobulin

	Renal disorder
Tubulointerstitial disease	Myeloma cast nephropathy
	Light chain proximal tubulopathy (with or without Fanconi syndrome)
Glomerular disease	
Organized deposits	Light chain (AL) amyloidosis
	Type I and II cryoglobulinemic glomerulonephritis
	Nonamyloid fibrillary glomerulonephritis
	GOMMID (or immunotactoid glomerulopathy)
Nonorganized deposits	Randall-type (MIDD)
	LCDD
	HCDD
	LHCDD
	Proliferative glomerulonephritis with monoclonal Ig deposits
	Waldenstrom macroglobulinemia

Abbreviations: GOMMID, glomerulonephritis with organized microtubular monoclonal Ig deposits; HCDD, heavy-chain deposition disease; Ig, immunoglobulin; LCDD, light chain deposition disease; LHCDD, light and heavy chain deposition disease; MIDD, monoclonal Ig deposition disease.

SCREENING FOR INTACT MONOCLONAL GAMMOPATHY

The most commonly used screening test for an intact immunoglobulin paraprotein is serum protein electrophoresis (SPEP), which through identification of an M-spike is sensitive for the detection of an immunoglobulin clone down to a concentration of 500 mg/l.

Immunofixation electrophoresis (IFE) is more sensitive than SPEP (150 mg/l), and it provides isotype characterization of a monoclonal gammopathy. However, IFE is labor-intensive, and it does not quantify the monoclonal immunoglobulin. Serum IFE is therefore generally used if there is an abnormality on SPEP or if there is a high clinical suspicion of a monoclonal gammopathy. Serum IFE is particularly useful in identifying and monitoring a pathological clone when there is more than one clone present.

SCREENING FOR FLC MONOCLONAL GAMMOPATHY

Although SPEP and IFE can detect a light chain clone at concentrations of >500 mg/l and >150 mg/l, respectively, the sensitivity is inadequate, as a clinically relevant monoclonal light chain may be present in the serum at levels below these thresholds. Additional screening assays are therefore needed and include the following:

(i) Urine assays

Because of the insensitivity of SPEP and IFE, urinary testing for light chain (Bence Jones proteinuria) has been the long-term standard of care for the screening and monitoring of a light chain clone. Light chains are physiologically concentrated into the urine, which can then be mechanically concentrated. Urinary protein electrophoresis (UPEP) and urine IFE (UIFE) are both used and can be sufficiently sensitive to identify an abnormal clone of light chain in the urine to a concentration of 10 mg/l.

The shortfalls in the use of a urine assay in clinical practice include the frequent failure to provide an appropriate 24-hour urine collection or a paired serum sample to accompany a urine collection.[6] Other important variables include the degree of urine concentration, the IFE method used, and the affinity of the polyclonal antibodies used in the IFE assay.[7] Furthermore, urine light chain concentrations may not necessarily correlate with serum concentrations, and they are therefore not directly related to tumor size and light chain production.[8]

(ii) Serum FLC assays

The first marketed assay used for quantifying serum FLC is a nephelometric assay (Freelite, Birmingham, UK) that uses rabbit anti-human polyclonal antibodies directed against epitopes that are hidden when the light chain is present in the intact immunoglobulin molecule and exposed when the light chain is present in a free form. The assay measures both isotypes of light chain, kappa and lambda, and the results are provided for both isotypes and the ratio of the isotypes. When interpreting the test, both the ratio and the level of each isotype should be considered. The FLC assay is highly sensitive and can detect both isotypes to levels that are below the normal physiological range.

As each cell of the B-cell lineage produces one isotype of light chain immunoglobulin, an excess production of that light chain will usually occur in clonal proliferation as compared with the other isotype. This excess leads to an abnormal FLC ratio. An elevated ratio indicates the presence of a kappa FLC clone, whereas a low ratio indicates a lambda FLC clone. The levels of clonal light chain can vary from several thousand–fold the upper limit of normal in some cases of multiple myeloma to a very subtle perturbation within the normal range of the ratio or within the measurement uncertainty of the assay in some cases of monoclonal gammopathy (see below).

Elevation of the levels of both serum FLC isotypes can occur as a consequence of immune activation or renal impairment, as the main route of clearance of light chain is through the kidneys (see below). However, in this setting, the ratio of the isotypes is maintained within a normal range. In the absence of clonal proliferation, the ratio of kappa to lambda light chain production is preserved at a constant rate of 2:1.

This nephelometric assay has enhanced the diagnostic accuracy and sensitivity of paraprotein-related disease and has been credited for: (i) the introduction of stringent complete response as a new criterion of multiple myeloma response; (ii) improved risk stratification in monoclonal gammopathy; (iii) the identification and characterization of light chain MGUS; and (iv) response criteria in immunoglobulin light chain amyloidosis.

In addition to Freelite, two other assays have been developed to date for FLC testing.