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BIOMEDICINA - PATOLOGIA CLINICA - INFORMATICA

Bence Jones Proteinuria

Operational Protocol to determine the presence of Bence Jones Proteins in Urine:

Proposal and Bibliographical List

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Introduction :

The ***Bence Jones Proteins (BJP)*** are by definition, ***MONOCLONAL FREE Light Chains (MFLC)*** [1, 5, 9, 11, 24, 35, 37]. When bibliography uses the terms Bence Jones Proteins, Light Chains, Free Light Chains, Kappa and Lambda Chains, etc., indistinctly, inaccurately and generating confusion, it is in fact making strict reference to the Bence Jones Proteins.

The ***BJP*** are indicators of a malignant process [1, 2, 3, 4, 5, 6, 8, 9, 11, 15, 37, 38, 39]. ***Their presence is demonstrated in 60-87% of Multiple Myeloma (MM)*** [2, 4, 9, 22, 38] **cases** and, ***in 15-20% of the MM cases it is the only biological product excreted by the malignant clone*** (Bence Jones, Light Chain or Micromolecular Myeloma) [2, 4, 9, 21, 23, 38].

Given its physiopathology, ***its presence in urine can be detected quicker and more easily than in serum*** [21, 35, 36, 38], except in case of a reduced Glomerular Filtration. Therefore, ***should Monoclonal Gammapthy be suspected, the patient's urine must be studied*** since it can demonstrate the presence of a monoclonal component in it, constituted by BJP, without any anomaly being observed in the serum of the same patient.

In themselves, the ***BJP*** are a "malignant entity" producing pathological effects mainly in the ***kidney*** [2, 4, 6, 8, 9, 13, 16, 17, 22, 25, 27, 28, 29, 30, 31, 32, 33, 34, 38]. The BJP are nephrotoxic and closely linked to the renal complications of the MM, where the second cause of death is kidney failure[38, 40]. Renal damage is frequently the first sympton leading to final diagnosis of MM [17, 26, 27, 38] and in addition it is an important prognosis factor influencing patient survival [5, 14, 16, 20, 22, 27, 40].

Periodical determination [2, 3, 4, 8, 38] of ***BJP presence and quantity*** in urine is an essential element for diagnosis [1, 5, 7, 9, 10, 11, 15, 24, 26, 36] (stage establishment, etc.), prognosis [2, 4, 7, 8, 9, 10, 11, 16, 17, 18, 20, 22, 26], evolution control and treatment response [1, 2, 4, 5, 7, 8, 9, 11, 12, 15, 19, 22, 23, 37, 38] of ***MM***.

The BJP search should foresee, for its composition confirmation, ***the use of an immunological method and***, to confirm its monoclonal distribution, ***the use of an electrophoretic method***, in addition to bearing in mind the following facts:

1.- On studying the urine, we can encounter any of the following proteins, or a mixture of them:
   - ***BJP*** (= MFLC)
   - Polyclonal Free Light Chains (PFLC)
   - Oligoclonal Free Light Chains or "Ladders"
   - ***Complete Immunoglobulins*** (monoclonal and/or polyclonal) (***IG's***)

2.- The presence of ***complete IG's*** in urine (accompanying the BJP or alone) is considerably more ***frequent*** than generally considered, particularly in patients with the glomerular function affected.

3.- Specific ***anti FLC*** antiserums only react with Light Chains when these are not a part of the complete IG's, i.e. when they are "***free***" (hence its name).

4.- The ***anti "Total"*** (free & bound) ***Light Chain*** antiserums (TLC) react with the Light Chains both when they are free and when they are bound forming part of the IG's, i.e. they ***react*** indistinctly with FLC and with ***complete IG's***.

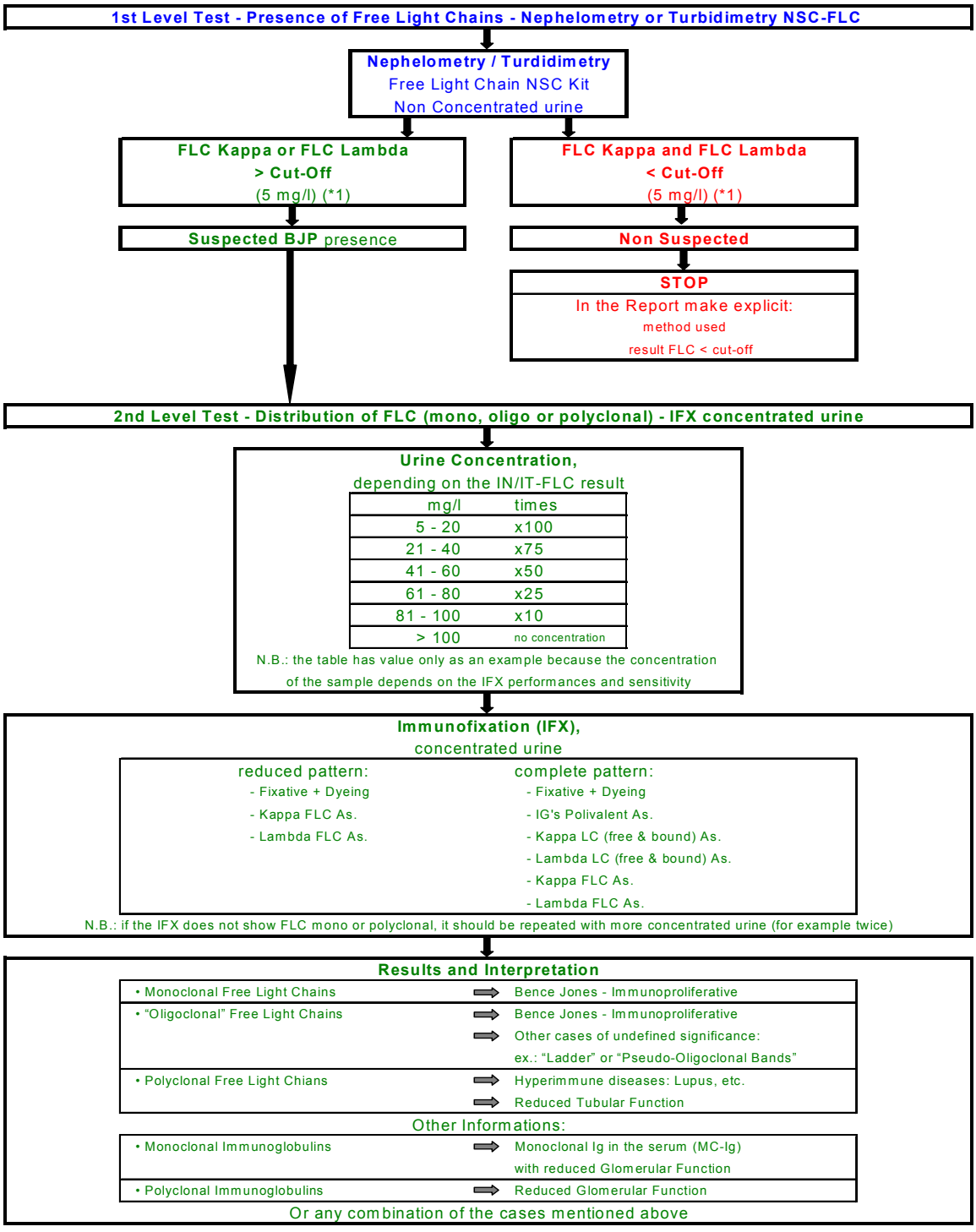
5.- The above factors have an impact both on the qualitative determination of the presence of BJP (=MFLC) in urine as in its dosage.

The proposed operational protocol on the following page plans the use of Nephelometry (or Turbidimetry) with specific anti FLC antiserums, as a first level immunological method whose objective is to evidence the presence of FLC in urine, and the use of Immunofixation, also with specific anti FLC antiserums, as an electrophoretic confirmation method whose purpose is to demonstrate or discard the monoclonality of the FLC evidenced with the Nephelometry. Only those samples with positive results on the first level test, Nephelometry, will be subjected to the confirmation test, Immunofixation.

Operational Protocol Proposal :

Protocol Outline

The operational protocol outlined below is an example of how to use the ImmunoPrecipitation in liquid phase method (Nephelometry or Turbidimetry) in the search for Bence Jones Proteins in urine, in a first diagnosis approach:



Note (*1): or other defined by the user

Notes

Note (*1) – Sample Type :

For the study of the FLC in general, and in particular the Bence Jones Proteins (BJP), different sample types are used without an agreement as to which is the most convenient. The most commonly used are:

- 24 hour urine
- first urine in the morning
- a random urine; often the second urine in the morning

The traditional sample is the 24 hour urine, which apart from the diuresis valuation, allows to avarage the presence of FLC during a reasonable time period.

Some propose the use of a random urine, often the second urine in the morning, because it is easy to obtain and because its contamination is more difficult, estimating diuresis via determination of the urinary Creatinine used to discard excessively diluted samples which could give False Negatives. This proposal presents greater convenience in obtaining and handling the sample, but ignores the very probable cyclical production of FLC (mentioned by several authors, although not proven for FCL it is for other proteins), which given its very short hemilife, would also determine variations in its urinary excretion, which could lead to samples close the sensitivity limit of the method used to false negative results, apart from making the quantitative measurement difficult in this kind of sample, even valuing the Creatinine as a diuresis estimation.

Use of the first urine in the morning does not provide anything new regarding another random urine, plus it is more susceptible to contamination.

Our opinion is that until demonstrated to the contrary, and above all if there is interest in the quantitative determination, the best thing is to use the 24 hour urine with Sodium Azide as a preservative to prevent eventual bacterial contamination.

Note (*2) - Discriminating Value :

The proposed discriminating value in the protocol, 5 mg/L (0.5 mg/dL), must be considered as an orientational proposal since it is the user who must determine the discriminating value to be used, according to the clinicians and coherent with the sensitivity of the confirmation method used (usually IFE).

In any event, the value proposed (5 mg/L) is below the related values in the bibliography (few authors dare to give specific values) which coincide that a sensitivity of around 10 mg/L is sufficient; moreover *Beetham* claimed in the conclusions on his article that "*all laboratories should be capable of detecting BJP of around 10 mg/L*", after demonstrating that 35% of the laboratories taking part in a study in Great Britain were unable to detect a BJP of 60 mg/L (6 mg/dL) (*Detection of Bence Jones Protein in Practice. R. Beetham - Ann Clin Biochem 2000; 37: 563-570*).

In the urine of normal patients, the BJP in particular should be absent and, in general terms, only traces of polyclonal FLC could be found. Consequently, any detectable FLC value should be considered potentially positive and its distribution (monoclonal or otherwise) confirmed with an Immunofixation, to discard the presence of BJP.

Anyway, the clinical significance of small amounts of BJP is neither established nor is there agreement. Furthermore, sensitivity of the nephelometric method has shown in some studies to be superior to that of ImmunoFixation used as confirmation. So, although the most purest election would be to use the nephelometric method sensitivity limit as discriminating value, in practice, the majority of users employ the proposed value of 5 mg/L (the lowest point of the calibration curve) or many even 10 mg/L, as detailed in the little bibliography available, as the discriminating value for the screening.

Note (*3) - Antiserums Used in the ImmunoFixation :

The usually used clasical serum type panel, foresee the use of the following antiserums: IgA, IgG, IgM, Kappa Chains (free & bound) and Lambda Chains (free & bound). The use of this panel in the urine may present interpretation complications, which may give rise to false negatives for the presence of BJP, as for example in those cases where the presence of a complete monoclonal Immunoglobulin masks the BJP band due to an apparent co-migration (a supposedly infrequent situation, because it is not normally controlled, but in practice it appears with significative frequence).

For the urine it is safer and therefore recommendable to use an alternative panel foreseeing the use of anti Free Light Chain antiserums: Polyvalent IG's, Kappa Chains (free & bound), Lambda Chains (free & bound), Free Kappa Chains and Free Lambda Chains.

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11. **Vegh Z, Otto S, Eckhardt S.** Monoclonal Free Light Chains in Urine and their significance in clinical diagnostics: are they really tumor markers ?. *J Clin Lab Anal, 4(6), 1990*
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Bibliographical List - Abstracts :

9. **Clinical applications of immunoglobulin free light chain estimations**
   Int J Clin Lab Res 1993;23(1):25-9 (ISSN: 0940-5437)
   Tillyer CR
   Department of Chemical Pathology, Royal Marsden Hospital, London, UK.
   The relevance of free light chain assays to diagnosis, staging, treatment and prognosis assessment in B-cell disorders (including myeloma, chronic lymphocytic leukaemia, and lymphoma), multiple sclerosis and diabetes is discussed and their actual and potential use is examined.

10. **BUN, Bence Jones protein, and chromosomal aberrations predict survival in multiple myeloma**
    Rinsho Ketsueki 1997 Dec;38(12):1254-62 (ISSN: 0485-1439)
    Okada K; Oguchi N; Shinohara K; Tamura N; Ishii K; Noguchi Y; Hayashi S; Yamamoto H; Takeichi M; Fujimoto H; Shirota T; Hayashi T
    Third Department of Internal Medicine, Tokyo Medical College.
    The prognostic significance of some clinical features in 41 patients with multiple myeloma (including 2 patients with plasma cell leukemia) from our institution was analyzed. Out of 14 variables isolated from the univariate analysis (P < 0.05), only three (BUN, Bence Jones protein, and chromosomal aberrations) were significant in the multivariate model (P < 0.05). Derived from these three variables, three subpopulations of patients were identified. The first group included 20 patients with a low risk of death and their median survival has not been reached. In particular, no one died during the first 60 months in this group. The second group also included 14 patients with an intermediate risk of death and a median survival of 49.2 months. The third group comprised seven patients with a high risk of death during 24 months after diagnosis and a median survival of 31.6 months (P < 0.0001). Finally, Durie & Salmon's myeloma staging system was demonstrated in the present series, and it showed prognostic validity for each stage (P < 0.0222). Compared with Durie & Salmon's staging system, our prognostic model for multiple myeloma was more useful to predict prognosis when applied to the present series.

11. **Monoclonal free light chains in urine and their significance in clinical diagnostics: are they really tumor markers?**
    J Clin Lab Anal 1990;4(6):443-8 (ISSN: 0887-8013)
    Vegh Z; Otto S; Eckhardt S
    National Institute of Oncology, Budapest, Hungary.
    Bence Jones proteins (monoclonal free light chains of immunoglobulins) are the earliest known biological markers of malignant cell dyscrasia; Bence Jones proteinuria is also present in many types of B cell-related neoplasms. Sometimes, it may also occur in Hodgkin's disease. In some cases, benign monoclonal gammapathy was found to be associated nontumorous diseases as well. The type of monoclonal light chain, the degree of polymerization, and the isoelectric point of the molecule may affect the course of the disease. Urine samples from 637 patients with true or suspected lymphoproliferative diseases were investigated over a 2-yr period by different immunochemical methods. Bence Jones proteinuria was identified in 71 cases by isoelectric focusing combined with immunofixation, while the pathological protein was detected only in 63 cases by conventional methods. Bence Jones proteins can be detected by this new method at a level below the sensitivity of conventional procedures. Bence Jones proteins in the urine may signal a malignant tumor or malignant transformation of an earlier disease. The early detection of monoclonal immunoglobulin light chains in the urine may be important in clinical diagnosis, therapy, and follow-up.

12. **Antitumor activity of thalidomide in refractory multiple myeloma**
    N Engl J Med 1999 Nov 18;341(21):1565-71 (ISSN: 0028-4793)
    Singhal S; Mehta J; Desikan R; Ayers D; Roberson P; Eddlemon P; Munshi N; Anaissie E; Wilson C; Dhodapkar M; Zeddis J; Barlogie B
    Myeloma and Lymphoma Program, South Carolina Cancer Center, University of South Carolina, Columbia, USA.
    BACKGROUND: Patients with myeloma who relapse after high-dose chemotherapy have few therapeutic options. Since increased bone marrow vascularity imparts a poor prognosis in myeloma, we evaluated the efficacy of thalidomide, which has antiangiogenic properties, in patients with refractory disease.
    METHODS: Eighty-four previously treated patients with refractory myeloma (76 with a relapse after high-dose chemotherapy) received oral thalidomide as a single agent for a median of 80 days (range, 2 to 465). The starting dose was 200 mg daily, and the dose was increased by 200 mg every two weeks until it reached 800 mg per day. Response was assessed on the basis of a reduction of the myeloma protein in serum or Bence Jones protein in urine that lasted for at least six weeks.
    RESULTS: The serum or urine levels of paraprotein were reduced by at least 90 percent in eight patients (two had a complete remission), at least 75 percent in six patients, at least 50 percent in seven patients, and at least 25 percent in six patients, for a total rate of response of 32 percent. Reductions in the paraprotein levels were apparent within two months in 78 percent of the patients with a response and were associated with decreased numbers of plasma cells in bone marrow and increased hemoglobin levels. The microvascular density of bone marrow did not change significantly in patients with a response. At least one third of the patients had mild or moderate constipation, weakness or fatigue, or somnolence. More severe adverse effects were infrequent (occurring in less than 10 percent of patients), and hematologic effects were rare. As of the most recent follow-up, 36 patients had died (30 with no response and 6 witha response). After 12 months of follow-up, Kaplan-Meier estimates of the mean (+/-SE) rates of event-free survival and overall survival for all patients were 22+/-5 percent and 58+/-5 percent, respectively.
    CONCLUSIONS: Thalidomide is active against advanced myeloma. It can induce marked and durable responses in some patients with multiple myeloma, including those who relapse after high-dose chemotherapy.

21. **Renal insufficiency due to light chain multiple myeloma**
Ned Tijdschr Geneeskd 2000 Nov 4;144(45):2133-7 (ISSN: 0028-2162)
van Zaanen HC; Diderich PP; Pegels JG; Ruizeveld de Winter JA
Sint Franciscus Gasthuis, afd. Inwendige Geneeskunde, Rotterdam.
In 3 female patients, aged 65, 83 and 76 years, with severe renal failure, light chain multiple myeloma was diagnosed, following a substantial delay on the part of the doctors concerned. Either the diagnosis had not suspected or the serum proteins had been misinterpreted. After a while, the first two patients declined further treatment with chemotherapy and haemodialysis, and subsequently died. The third patient attained a creatinine clearance of 20 ml/min and was subsequently treated for the multiple myeloma in the outpatients department. The absence of a paraprotein peak in the serum does not exclude the possibility of a multiple myeloma. In the case of light chain disease, the gammaglobulin region is, in fact, often empty. Treatment of multiple myeloma consists of a rapid rehydration and forced diuresis; the usefulness of plasmapheresis has not been demonstrated.

22. **The kidney in multiple myeloma. The physiopathological and clinical aspects**
Recenti Prog Med 1994 Feb;85(2):123-33 (ISSN: 0034-1193)
Vivaldi P; Comotti C; Pedrazzoli M
UO Medicina 2o, Istituto Ospedaliero S. Chiara, Trento.
The renal concern in a multiple myeloma (MM) case has a frequency of 50% and causes a worsening of the disease with a survival average of about 12 months. The monoclonal light free chains (CLL) produced in excess by the plasmacytes are present in the urine as proteinuria of Bence Jones (PBJ) in 60-70% of patients affected by MM. They represent the major pathogenetic factor of the nephropathy in course of MM as they can deposit in shape of intratubular "casts" in the myeloma casts nephropathy (MCN). In some worse cases, dehydration or hypercalcaemia can cause an irreversible acute renal insufficiency (RI). It is therefore important in a patient affected with MM with PBJ to prevent, locate and opportunely treat these situations which worsen the nephropathy. Beside the tubular cast nephropathy, the CLL "accumulate" in the kidney even though with a lower frequency compared to MCN, in the light chains deposition disease (LCDD) and in the amyloidosis AL (AL). LCDD is characterized by a deposit of nodular amorphous materials PAS positive in the glomerulus and sometimes even in the tubulus. It usually presents itself as a chronic RI and a proteinuria causing nephrotic syndrome (NS). This quickly evolves into uraemia and its evolution can be lessened by the MM treatment. AL in course of MM also reeals with a chronic RI and NS. CLLs deposit in the typical fibrillar structure, on the vessel walls, in the glomerulus, in the mesangium and can be marked out with the Congo red colouring and the subsequent green birefringence through microscope with polarized light. Prognosis of AL is extremely severe and no benefit is given by the treatment of the hematological illness. It is therefore absolutely necessary to study the renal histology through biopsy when MM is grade B, that is, with serumal creatinine above 2 mg/dl as: MCN imposes the MM treatment programme in order to reduce the tubular excess of PBJ and to attempt to make RI reversible; MCN with tubular atrophy and interstitial fibrosis results in an unfavourable prognosis as it expresses a nephropathic irreversibility due to the loss nephrons. It will therefore necessary to start on a renal substitutional treatment programme. Renal damage in course of MM is not always tubular, rather an unexpected glomerular damage of LCDD or amyloidosis AL type can be found.(ABSTRACT TRUNCATED AT 400 WORDS).

23. **Immunoturbidimetric assay for estimating free light chains of immunoglobulins in urine and serum.**
J Clin Pathol 1991 Jun;44(6):466-71 (ISSN: 0021-9746)
Tillyer CR; Iqbal J; Raymond J; Gore M; McIlwain TJ
Department of Chemical Pathology, Royal Marsden Hospital, Sutton, Surrey.
An immunoturbidimetric assay for the assessment of free kappa and lambda light chains of immunoglobulins was developed using a commercial polyclonal antiserum with reactivity towards epitopes on the light chains, which are not expressed when they are bound to heavy chains. The assay, on a centrifugal analyser, is simple and rapid. The limit of detection is 5 mg/l of free light chain, with an assay range of 5-120 mg/l, intrabatch precisions from 1.5-6.4%, and interbatch precisions from 6.5-8.9%. The assay was only slightly less sensitive than colloidal gold staining of cellulose acetate electrophoreses for the detection of Bence-Jones protein in urine. For the serial monitoring of response to chemotherapy in patients with myeloma, the assay correlated well with serum paraprotein estimates obtained by densitometric scanning of Ponceau stained cellulose acetate electrophoreses, but not with serum beta-2 microglobulin measurements, even after correction for the effects of creatinine. These assays may prove to be of use for the monitoring of tumour response in the treatment of Bence-Jones myeloma.

24. **Clinical applications of immunoglobulin free light chain analysis**
Int J Clin Lab Res 1994;24(2):120-1 (ISSN: 0940-5437)
Pascali E
The potential of immunoglobulin-free light chain detection and measurement in biological fluids, and particularly in urine, has not yet been fully explored in clinical medicine, because of differences in sensitivity and lack of standardization of both quantitative assays and qualitative analysis. The ability to identify monoclonal free light chain, i.e., Bence-Jones protein, reliably in urine is of great clinical interest even when it occurs only in such small amounts that they frequently remain undetected by the routine methods used in many laboratories. The standardized adoption of both qualitative and quantitative procedures with comparable sensitivity is suggested to allow precise characterization of the clonal nature, and therefore the clinical role, of any free light chain excess.