

### **Freelite<sup>TM</sup> / Hevylite<sup>TM</sup> Issue**

**The International Myeloma Foundation** (*IMF*) presents this special edition of CITINGS, our premiere publication featuring the most up-to-date information on myeloma treatment and supportive care. This edition focuses on the Freelite<sup>®</sup> test, an established immunoassay panel that analyses free light chains, as well as the new Hevylite<sup>TM</sup> test, a novel immunoassay panel that analyses beavy chain/light chain pairs, and references publications available since ASH 2010.

It is our bope that CITINGS will help keep you abreast of the latest developments in myeloma treatment. As always, we welcome your feedback; you may contact the IMF at (800) 452-CURE (2873) or at our website myeloma.org.

- Susie Novis, President, IMF

### Serum Free Light Chain Assays Publications November 2010 – May 2011

#### **(Where a set of the s**

López-Anglada L, Puig N, Díez-Campelo M, Alonso-Ralero L, Barrena S, Aparicio MA, Gutiérrez NC, García-Sanz R. *Ann Clin Biochem. 2010 Nov;47(Pt 6):570-2. [Epub 2010 Oct 7.]* 

#### http://www.ncbi.nlm.nih.gov/pubmed/20930031

This case report illustrates a new case of gamma-heavy chain disease, in which serum free light-chain analysis and flow cytometry represent a valuable tool for diagnosis, a finding that could be very important for the future management of these patients.

Heavy chain diseases (HCDs) are rare B-cell lymphoproliferative neoplasias characterized by the production of a monoclonal component consisting of a truncated monoclonal Ig heavy chain without the associated light chain. Among them, patients with gamma-HCD are so rare that no more than 150 cases can be found in the literature. In this paper, we report one additional case: an 83-year-old man with a gamma-HCD, in whom a kappa light chain component was detected in the serum by using the serum free light-chain assessment and in addition monoclonal kappa cytoplasmic expression was detected in bone marrow plasma cells by flow cytometric analysis. In the work-up of the patient, the underlying anatomopathological lymphoproliferative disease corresponded to a lymphoplasmacytic lymphoma, as it is stated in the current World Health Organization classification (2008), with both lymphadenopathic and bone marrow infiltration. As in other cases, several autoimmune manifestations (antiphospholipidic syndrome and immune thrombocytopenia) were present during the course of the disease in this patient. This case report illustrates a new case of gamma-HCD, in which serum free light-chain analysis and flow cytometry represented a valuable tool for diagnosis, a finding that could be very important for the future management of these patients.

### Coexistence of myeloma cast nepbropatby, light chain deposition disease, and non-amyloid fibrils in a patient with multiple myeloma.

Qian Q, Leung N, Theis JD, Dogan A, Sethi S. *Am J Kidney Dis. 2010 Nov;56(5):971-6. [Epub 2010 Sep 25.]* http://www.ncbi.nlm.nih.gov/pubmed/20870327

The authors describe the unusual kidney biopsy findings of concurrent myeloma cast nephropathy and glomerular non-amyloid fibrillary deposits composed of immunoglobulin G heavy chains and  $\lambda$  light chains in a patient with multiple myeloma who presented with acute renal failure. They show that laser microdissection and mass spectrometry is an extremely useful ancillary test for the diagnosis of heavy and light chain deposition diseases.

Plasma cell dyscrasias can present as myeloma cast nephropathy, AL amyloid, or light chain deposition disease. We describe the unusual kidney biopsy findings of concurrent myeloma cast nephropathy and glomerular non-amyloid fibrillary deposits composed of immunoglobulin G (IgG) heavy chains and  $\lambda$  light chains in a patient with multiple myeloma who presented with acute renal failure. We performed laser microdissection

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and mass spectrometry-based proteomic analysis, which showed that the fibrillary deposits likely contained Ig $\gamma$ 1 constant region and  $\lambda$  light chain constant region, whereas  $\kappa$  light chains and serum amyloid P proteins were absent. Treatment of multiple myeloma resulted in resolution of the renal manifestations, suggesting a common underlying mechanism for the cast nephropathy and heavy and light chain deposition disease. We show that laser microdissection and mass spectrometry is an extremely useful ancillary test for the diagnosis of heavy and light chain deposition diseases.

### Serum immunoglobulin free light-chain measurement in primary amyloidosis: prognostic value and correlations with clinical features.

Kumar S, Dispenzieri A, Katzmann JA, Larson DR, Colby CL, Lacy MQ, Hayman SR, Buadi FK, Leung N, Zeldenrust SR, Ramirez-Alvarado M, Clark RJ, Kyle RA, Rajkumar SV, Gertz MA.

Blood. 2010 Dec 9;116(24):5126-9. [Epub 2010 Aug 26.]

http://www.ncbi.nlm.nih.gov/pubmed/20798235

The authors study the relationship between free light chain (FLC) levels and clinical features in 730 patients with newly diagnosed amyloidosis (AL). They find that the type of light chain impacts the spectrum of organ involvement and the FLC burden correlates with survival in AL.

Immunoglobulin free light chains (FLC) are the precursors of amyloid fibrils in primary amyloidosis (AL). We studied the relationship between FLC levels and clinical features in 730 patients with newly diagnosed AL. The plasma cell clone was lambda in 72% patients, and kappa in 28% patients. kappa-AL had more GI tract and liver involvement, whereas renal involvement was more with lambda-AL. While the overall survival (OS) was similar for kappa and lambda-AL, the median OS for those without an identifiable serum heavy chain was significantly shorter (12.6 vs. 29.9 months; P=0.02). The OS was shorter among those with a higher dFLC (involved FLC - uninvolved FLC; kappa>29.4 mg/dL or lambda>18.2 mg/dL using median for cutoff); 10.9 vs. 37.1 months; P<0.001. In multivariate analysis, dFLC was independent of other prognostic factors. The type of light chain impacts the spectrum of organ involvement and the FLC burden correlates with survival in AL.

#### > Mass spectrometry-based proteomic diagnosis of renal immunoglobulin beavy chain amyloidosis.

Sethi S, Theis JD, Leung N, Dispenzieri A, Nasr SH, Fidler ME, Cornell LD, Gamez JD, Vrana JA, Dogan A. *Clin J Am Soc Nephrol. 2010 Dec;5(12):2180-7. [Epub 2010 Sep 28.]* 

http://www.ncbi.nlm.nih.gov/pubmed/20876678

The authors describe the use of laser microdissection (LMD) and mass spectrometry (MS)-based proteomic analysis for the accurate typing of 14 cases of amyloidosis, as well as the clinicopathologic findings of four problematic cases of renal Ig heavy chain amyloidosis that required LMD/ MS proteomic analysis for accurate typing of the amyloid. They conclude that LMD/MS is a sensitive and specific tool for diagnosis and accurate typing of renal amyloidosis, including Ig heavy chain amyloid.

BACKGROUND AND OBJECTIVES: Amyloidosis is a group of disorders characterized by accumulation of extracellular deposition of proteins as insoluble aggregates. The clinical management of amyloidosis is based on identifying the underlying etiology and accurate typing of the amyloid. Ig heavy chain amyloid involving the kidney is poorly recognized and often poses a diagnostic dilemma. DESIGN, SETTING, PARTICIPANTS, & MEASURES: In this study, we describe the use of laser microdissection (LMD) and mass spectrometry (MS)-based proteomic analysis for the accurate typing of 14 cases of amyloidosis. We also describe the clinicopathologic findings of four problematic cases of renal Ig heavy chain amyloidosis that required LMD/MS proteomic analysis for accurate typing of the amyloid. RESULTS: LMD/MS proteomic data of four cases of Ig heavy chain renal amyloidosis showed Ig heavy chains with or without light chains. The break up of the Ig heavy chains was as follows: one case showed Ig $\gamma$ 1 chain constant region and  $\lambda$  light chains, one case showed Ig $\alpha$  chain constant region and  $\kappa$  light chains. We compare the LMD/ MS proteomic data of Ig heavy chain renal amyloid with that of other types of amyloid, including Ig light chains, serum amyloid A, fibrinogen A- $\alpha$  chain renal amyloid, and transthyretin amyloid. CONCLUSIONS: We conclude that LMD/MS is a sensitive and specific tool for diagnosis and accurate typing of renal amyloidosis, including Ig heavy chain amyloid.

#### Use of serum free light chain analysis and urine protein electrophoresis for detection of monoclonal gammopathies.

Holding S, Spradbery D, Hoole R, Wilmot R, Shields ML, Levoguer AM, Doré PC.

Clin Chem Lab Med. 2011 Jan;49(1):83-8. [Epub 2010 Oct 20.]

http://www.ncbi.nlm.nih.gov/pubmed/20961192

The authors assess the effect of replacing urine protein electrophoresis (UPE) with serum free light chain (FLC) analysis and find that using FLC alongside or in place of UPE can give clinical benefit through earlier diagnosis, and hence treatment earlier in the disease for patients with patients with monoclonal gammopathies.

Abstract Background: Serum free light chain (FLC) analysis is used in the prognostic assessment and monitoring of patients with monoclonal gammopathies (MG). Its use in detection of MG is less widespread despite good sensitivity for diseases poorly detected by serum protein electrophoresis (SPE), e.g., FLC disease and AL amyloidosis. FLC analysis may facilitate earlier diagnosis in these diseases. However, if replacing urine protein electrophoresis (UPE) in an initial screening algorithm, this must be balanced against any loss of detection of Bence Jones proteinuria (BJP). Methods: We assessed the effect of replacing UPE with FLC. Sensitivity of FLC for BJP was assessed in 126 clinical cases where UPE and FLC analyses were performed. Impact on disease detection was assessed from 753 patient sera tested by SPE and FLC and 128 patients matched associated urine samples. Results: Sensitivity of FLC for BJP was 98%. Use of FLC in routine testing increased the number of MG detected by 7%. Conclusions: Using FLC alongside or in place of UPE can give clinical benefit through earlier diagnosis and hence treatment earlier in the patients' disease.

## Sixth International Symposium on clinical applications of serum free light chain analysis, Bath, England, 23-24 September 2010. [Article in French]

Decaux O. *Rev Med Interne. 2011 Jan;32(1):64-6. [Epub 2010 Dec 3.]* http://www.ncbi.nlm.nih.gov/pubmed/21126805 **No abstract available.** 

#### Serum free light chain analysis in multiple myeloma and plasma cell dyscrasias.

Ozsan GH, Dispenzieri A.

*Expert Rev Clin Immunol. 2011 Jan;7(1):65-73.* http://www.ncbi.nlm.nih.gov/pubmed/21162651

### This article summarizes the recent studies and highlights the importance of free light chain analysis in the diagnosis of plasma cell dyscrasias, its prognostic value, and its role in the management of this group of diseases.

After the development of a reliable method to detect free light chains in serum, several investigations have been conducted to explore their importance in plasma cell dyscrasias (PCD). Detection of monoclonal proteins is very important in the diagnosis and management of PCD, which include a broad spectrum of diseases such as multiple myeloma and also benign, premalignant disorders like monoclonal gammopathy of undetermined significance. The aim of this article is to summarize the recent studies and to highlight the importance of free light chain analysis in the diagnosis of PCD, its prognostic value and role in the management of this group of diseases.

#### () Interlaboratory study of free monoclonal immunoglobulin light chain quantification.

Vávrová J, Maisnar V, Tichý M, Friedecký B, Čermáková Z, Dastych M, Gottwaldová J, Kučera P, Krotká J, Racek J, Ženková J, Schneiderka P, Lochman P, Zima T, Benáková H, Büchler T, Spáčilová J, Hájek R, Palička V.

Clin Chem Lab Med. 2011 Jan;49(1):89-92. [Epub 2010 Oct 29.]

http://www.ncbi.nlm.nih.gov/pubmed/21034251

The authors initiate an interlaboratory study measuring free light chain (FLC) concentrations in 12 serum samples from patients with monoclonal gammopathies. They find that, due to its impact on the clinical management of patients with gammopathy, FLC quantification needs to become a part of the regular quality control cycle in myeloma centers.

Abstract Background: Quantification of monoclonal immunoglobulin free light chains (FLCs) in serum is used increasingly in clinical practice for the diagnosis, prognostic assessment, and treatment monitoring of monoclonal gammopathies. It is used as an adjunct to standard serum protein electrophoresis and immunofixation. However, methods for FLC quantification need further standardization and validation. Methods: The Czech Myeloma Group and the Czech Society of Clinical Biochemistry have initiated an interlaboratory study where six laboratories collaborating with the primary myeloma treatment centres measured FLC concentrations in 12 serum samples from patients with monoclonal gammopathies. Results: Repeatability of the measurements in five laboratories was calculated based on differences between the results of duplicate measurements. We found that repeatability depended more on the laboratory than on the device used for measurement. Conclusions: The study revealed several weak points in the methodology, including the need for a uniform sample dilution procedure. Interlaboratory reproducibility was comparable with values achieved in the NEQAS programme. Because the  $\kappa/\lambda$  ratio cannot be measured with high precision,  $\kappa$  and  $\lambda$  FLC concentrations should be used where possible. Due to its impact on the clinical management of patients with gammopathy, FLC quantification needs to become a part of the regular quality control cycle in myeloma centres.

#### Novel M-Component Based Biomarkers in Waldenström's Macroglobulinemia.

Leleu X, Koulieris E, Maltezas D, Itzykson R, Xie W, Manier S, Dulery R, Boyle E, Gauthier J, Poulain S, Tatiana T, Panayiotidis P, Bradwell AR, Harding S, Leblond V, Kyrtsonis MC, Ghobrial IM.

Clin Lymphoma Myeloma Leuk. 2011 Feb 1;11(1):164-7.

http://www.ncbi.nlm.nih.gov/pubmed?term=hevylite

#### The authors summarize studies conducted to delineate the role of the Freelite® test and the Hevylite test® in Waldenstrom's macroglobulinemia.

Waldenstrom's macroglobulinemia (WM) is an indolent B-cell lymphoma of the lymphoplasmacytic type accompanied by a serum IgM component. However, conventional IgM quantification lacks sensitivity, does not precisely reflect tumor burden of WM, and, although being the main marker for monitoring response to treatment, may not be accurate. New serum M-component based biomarkers were developed for routine practice in recent years, such as the Freelite® test and more recently the Hevylite® test. Studies have shown that Freelite was a prognostic marker for time to treatment in WM that helps monitoring disease response or progression. Hevylite measures IgM-kappa and IgM-lambda, separately, and might provide true quantitative measurement of the IgM M-spike. Although current data are preliminary, Hevylite might replace the current technique to measure IgM M-spike in the years to come. We summarize herein studies conducted to delineate the role of these tests in WM.

#### Renal failure in multiple myeloma: a medical emergency. Wirk B.

Bone Marrow Transplant. 2011 Feb 21. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/21339749

#### The authors discuss newly diagnosed plasma cell myeloma, including that the serum free light chain assay and serum $\beta$ -2-microglobulin free heavy chain assay are now being used to rapidly diagnose plasma cell myeloma in renal failure and provide prognostic information in the setting of renal failure where the Durie-Salmon and International Staging Systems do not.

Up to 50% of newly diagnosed plasma cell myeloma (PCM) patients can present with renal insufficiency, 20% with severe renal impairment and 10% requiring dialysis. PCM patients account for 2% of the dialysis population, adding 5000 new patients each year worldwide. Dialysisdependent PCM patients have a 2.77 higher risk of death compared with other dialysis-dependent patients without this diagnosis. Renal failure and especially dialysis dependency is an independent poor prognostic factor in PCM, with the majority unable to achieve dialysis independence. Renal failure in PCM is a medical emergency with the need for rapid accurate diagnosis and prompt institution of supportive care and PCMdirected therapy, because reversal of renal impairment and recovery from dialysis dependency can occur in up to half the patients early in the course of disease and can lead to enormous survival benefits. Recently, the serum free light chain (SFLC) assay and serum  $\beta$ -2-microglobulin free heavy chain (SFHC) assay have been used to rapidly diagnose PCM in renal failure and provide prognostic information in the setting of renal failure where the Durie-Salmon and International Staging Systems do not. A renal biopsy early in the course of renal impairment can provide diagnostic and prognostic information. A new generation of dialyzers with larger pores than routine dialyzers can be used with extended hemodialysis to remove SFLC more efficiently than plasmapheresis, allowing for greater renal recovery. Novel chemotherapy agents such as bortezomib are associated with an improved renal response and have moved to the front line of therapy. Successful use of high-dose therapy and autologous hematopoietic cell transplantation (HCT) in PCM with renal failure and even dialysis dependency has been associated with late renal recovery and also allowed for the subsequent use of renal transplantation to provide even greater survival benefits. Combined non-myeloablative allogeneic HCT with renal transplant in PCM patients with end-stage renal disease on dialysis is now being studied in prospective trials.

### Transplantation vs. conventional-dose therapy for amyloidosis.

Palladini G, Merlini G.

Curr Opin Oncol. 2011 Mar;23(2):214-20.

#### http://www.ncbi.nlm.nih.gov/pubmed/21178616

This review focuses on the role of autologous stem cell transplantation and conventional-dose therapy in light of advances in risk stratification and amyloidosis patient monitoring. Among the recent findings discussed is that the possibility of directly measuring the amyloidogenic precursor, the circulating free light chain, improves monitoring response to therapy.

PURPOSE OF REVIEW: Multiorgan involvement renders patients with AL amyloidosis particularly susceptible to treatment toxicity. The introduction of autologous stem cell transplantation (ASCT) represented a major advancement, but was associated with unacceptable toxicity in high-risk patients. Thus, efforts were made to improve the eligibility criteria for ASCT and to design novel, more effective, conventional-dose regimens. This review focuses on the role of ASCT and conventional-dose therapy in light of advances in risk stratification and patient monitoring. RECENT FINDINGS:

The possibility of directly measuring the amyloidogenic precursor, the circulating free light chain (FLC), improved monitoring response to therapy. Cardiac biomarkers, N-terminal pro-natriuretic peptide type-B (NT-proBNP) and troponins (cTn) allow the most accurate prognostic stratification and direct the choice of therapy. Serial measurement of NT-proBNP, cTn and FLC are used to rapidly assess treatment efficacy. Bortezomib and immune-modulatory drugs are going to play a major role in conventional-dose therapy and as adjuvant treatment after ASCT. SUMMARY: The choice between ASCT and conventional-dose chemotherapy is based on accurate risk assessment. Tight monitoring of hematologic and cardiac response is the cornerstone of treatment. Upcoming randomized trials will redefine the role of available therapies, assisting in the choice of the growing number of active regimens.

### (a) A novel approach for the purification and proteomic analysis of pathogenic immunoglobulin free light chains from serum.

Lavatelli F, Brambilla F, Valentini V, Rognoni P, Casarini S, Di Silvestre D, Perfetti V, Palladini G, Sarais G, Mauri P, Merlini G. Biochim Biophys Acta. 2011 Mar;1814(3):409-19. [Epub 2011 Jan 4.]

http://www.ncbi.nlm.nih.gov/pubmed/21215335

The authors develop an immunopurification approach to isolate serum free light chains (FLC) from patients with monoclonal gammopathies, followed by proteomic characterization. They conclude that this method is a novel instrument for studying the molecular bases of FLC pathogenicity, allowing for the first time the punctual biochemical description of the circulating forms.

An excess of circulating monoclonal free immunoglobulin light chains (FLC) is common in plasma cell disorders. A subset of FLC, as amyloidogenic ones, possess intrinsic pathogenicity. Because of their complex purification, little is known on the biochemical features of serum FLC, possibly related to their pathogenic spectrum. We developed an immunopurification approach to isolate serum FLC from patients with monoclonal gammopathies, followed by proteomic characterization. Serum monoclonal FLC were detected and quantified by immunofixation and immunonephelometry. Immunoprecipitation was performed by serum incubation with agarose beads covalently linked to polyclonal anti- $\kappa$  or  $\lambda$ FLC antibodies. Isolated FLC were analyzed by SDS-PAGE, 2D-PAGE, immunoblotting, mass spectrometry (MS). Serum FLC were immunoprecipitated from 15 patients with AL $\lambda$  amyloidosis (serum  $\lambda$  FLC range: 98-2350mg/L), 5 with AL $\kappa$  amyloidosis and 1 with  $\kappa$  light chain (LC)

myeloma ( $\kappa$  FLC range: 266-2660mg/L), and 3 controls. Monoclonal FLC were the prevalent eluted species in patients. On 2D-PAGE, both  $\lambda$  and  $\kappa$  FLC originated discrete spots with multiple pI isoforms. The nature of eluted FLC and coincidence with the LC sequence from the bone marrow clone was confirmed by MS, which also detected post-translational modifications, including truncation, tryptophan oxidation, cysteinylation, peptide dimerization. Serums FLC were purified in soluble form and adequate amounts for proteomics, which allowed studying primary sequence and detecting post-translational modifications. This method is a novel instrument for studying the molecular bases of FLC pathogenicity, allowing for the first time the punctual biochemical description of the circulating forms.

### Changes in serum-free light chain rather than intact monoclonal immunoglobulin levels predicts outcome following therapy in primary amyloidosis.

Kumar SK, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, Zeldenrust SR, Tan T, Sinha S, Leung N, Kyle RA, Rajkumar SV, Gertz MA.

Am J Hematol. 2011 Mar;86(3):251-5. doi: 10.1002/ajh.21948. [Epub 2011 Feb 15.]

http://www.ncbi.nlm.nih.gov/pubmed/21328431

This current study supports the notion that free light chain (FLC) response is a more useful measure of hematological response than M-protein response. It also highlights the importance of achieving at least a 90% reduction in the uninvolved FLC to improve the outcome of patients with light-chain amyloidosis.

Current response criteria for light-chain amyloidosis (AL) relegate FLC response to a subsidiary status relative to serum M-protein response. Given that light chains form the substrate for amyloid fibril formation, we hypothesized that changes in FLC might better predict outcome compared to changes in intact immunoglobulin levels. Two patient cohorts were studied, 347 patients who underwent an autologous stem-cell transplant (SCT) and 96 patients treated with melphalan/dexamethasone. We identified the lowest value following therapy for intact serum M-protein and the difference between involved and uninvolved FLC (FLC-diff). We first examined the relative contribution of M-protein and FLC-diff on the overall survival (OS), and found that FLC reduction, rather than M-protein reduction, significantly impacted OS. The median OS was not reached among those with a 50% decrease in FLC-diff compared to 20 months for the remainder. On regression analysis, a 90% reduction in FLC-diff following SCT best predicted being alive at 3 or 5 years. The median OS among those with a 90% decrease was not reached compared to 37.4 months for the rest P < 0.001. The current study supports the notion that FLC response is a more useful measure of hematological response than M-protein response. It also highlights the importance of achieving at least a 90% reduction in the FLC-diff to improve the outcome of patients with light-chain AL.

#### Serial serum free light chain measurements do not detect changes in disease status earlier than electrophoretic M-spike measurements in patients with intact immunoglobulin myeloma.

Uljon SN, Richardson PG, Schur PH, Anderson KC, Tanasijevic MJ, Lindeman NI.

Clin Chim Acta. 2011 Mar 18;412(7-8):562-8. [Epub 2010 Dec 7.]

http://www.ncbi.nlm.nih.gov/pubmed/21144845

In this study, the authors find that with 16 of 17 intact immunoglobulin myeloma patients tested frequently over approximately 3 years, serum free light chains perform no better than M-spike and do not add value to conventional serum electrophoresis.

BACKGROUND: Serum free light chains (SFLC) are used to manage patients with light chain or hyposecretory myeloma, and may also be useful in patients with intact immunoglobulin myeloma (IIMM), because their shorter half-life may enable earlier indication of relapse/response than electrophoretic M-spikes or heavy chain (IgGA) immunonephelometry. METHODS: One thousand five SFLC, M-spike, and IgGA concentrations were compared at multiple time points during the treatment of 17 myeloma patients, followed over 7.7-63.4months. Changes in these analytes were evaluated in context with changes in disease status and treatment. RESULTS: 14/17 (82%) patients showed synchrony between M-spike, IgGA, and SFLC measurements. SFLC changes preceded M-spike/IgGA in 1 patient, and lagged behind M-spike/IgGA in 2 patients. In eight patients, SFLC showed short-term fluctuations unaccompanied by changes in M-spike, IgGA, or clinical treatment. CONCLUSIONS: In 16/17 intact immunoglobulin myeloma patients tested frequently over ~3years, SFLC performed no better than M-spike and did not add value to conventional serum electrophoresis.

#### Immunoglobulin free light chain dimers in human diseases.

Kaplan B, Livneh A, Sela BA.

ScientificWorldJournal. 2011 Mar 22;11:726-35.

http://www.ncbi.nlm.nih.gov/pubmed/21442150

### This review focuses on the disease-related changes of the structure and level of dimeric free light chains, and raises the questions regarding their formation, function, and role in the pathogenesis and diagnosis of human diseases.

Immunoglobulin free light chain (FLC) kappa ( $\kappa$ ) and lambda ( $\lambda$ ) isotypes exist mainly in monomeric and dimeric forms. Under pathological conditions, the level of FLCs as well as the structure of monomeric and dimeric FLCs and their dimerization properties might be significantly altered. The abnormally high fractions of dimeric FLCs were demonstrated in the serum of patients with multiple myeloma (MM) and primary systemic amyloidosis (AL), as well as in the serum of anephric patients. The presence of tetra- and trimolecular complexes formed due to dimerdimer and dimer-monomer interactions was detected in the myeloma serum. Analysis of the amyloidogenic light chains demonstrated mutations within the dimer interface, thus raising the possibility that these mutations are responsible for amyloidogenicity. Increased  $\kappa$  monomer and dimer

levels, as well as a high  $\kappa/\lambda$  monomer ratio, were typically found in the cerebrospinal fluid from patients with multiple sclerosis (MS). In many MS cases, the elevation of  $\kappa$  FLCs was accompanied by an abnormally high proportion of  $\lambda$  dimers. This review focuses on the disease-related changes of the structure and level of dimeric FLCs, and raises the questions regarding their formation, function, and role in the pathogenesis and diagnosis of human diseases.

#### Regarding the Overestimation of Serum {kappa} Free Light Chains.

Levinson SS. *Clin Chem. 2011 May*;57(5):775-7. [Epub 2011 Feb 8.] http://www.ncbi.nlm.nih.gov/pubmed/21303911 No abstract available.

#### The role of serum immunoglobulin free light chain in response and progression in waldenstrom macroglobulinemia.

Clin Cancer Res. 2011 May 1;17(9):3013-8. [Epub 2011 Mar 17.] Leleu X, Xie W, Bagshaw M, Banwait R, Leduc R, Roper N, Weller E, Ghobrial IM. http://www.ncbi.nlm.nih.gov/pubmed/21415221

The authors seek to examine the role of serum free light chain (sFLC) in response and progression of patients with Waldenstrom macroglobulinemia and find that involved sFLC may be a useful marker of tumor measurement, showing earlier response and progression compared with IgM or M-spike measurements.

Introduction: The serum free light chain (sFLC) has been widely used in the assessment of response in patients with multiple myeloma and other plasma cell dyscrasias. However, its use in Waldenstrom macroglobulinemia (WM) has not been previously assessed. We sought to examine the role of sFLC in response and progression of patients with WM. Methods: This study was conducted in a cohort of 48 patients with a diagnosis of WM, untreated (n = 20) or relapsed/refractory (n = 28), prospectively treated on a bortezomib and rituximab trial. RESULTS: Involved FLC (iFLC) response occurred in 79% patients versus 60% by M-spike protocol criteria. The median time to response was shorter with iFLC than per protocol (2.1 and 3.7 months; P = 0.05). Progression defined using iFLC also correlated well to progression in the protocol ( $\kappa = 0.63$ ). However, the median time to progression (TTP) was more rapid by iFLC than per protocol (13.7 and 18.9 months). We also confirmed that a flare in iFLC in post-rituximab therapy did not correlate with lack of response or shorter TTP. CONCLUSION: Involved sFLC may be a useful marker of tumor measurement, showing earlier response and progression compared with IgM or M-spike measurements.

#### Atypical imaging feature of Non-secretory multiple myeloma.

Neeravari A, Netravati P, Mohammed R, Ragupathi AR, Nagarajappa AH. Ann Diagn Pathol. 2011 May 3. [Epub ahead of print.] http://www.ncbi.nlm.nih.gov/pubmed/21546295

The authors describe the case of a 23 year-old female with a rare case of non-secretory myeloma, presenting with bilateral limb weakness of two years duration. They find, in treatment, that free light chain assay (FLC) when used in complement with protein electrophoresis (PEP) and immunofixation electrophoresis (IFE) are pivotal in diagnosis of non-secretory multiple myeloma or light chain myelomas; FLC is a useful monitoring tool because it reflects therapy results due to short serum half-life.

Non-secretory multiple myeloma (NSMM) is a rare variant of the classic form of multiple myeloma in which no monoclonal gammopathy can be demonstrated in the serum or urine. We describe a rare case of non-secretory multiple myeloma in a 23 year old female presenting with bilateral limb weakness of two years duration. Clinically she was diagnosed to have Pott's spine and was treated with category 1 anti-tubercular drugs. Hematological investigations showed plasmacytosis and radiography showed osteolytic lesions. No monoclonal gammopathy was found in the serum or urine. MRI showed multiple compressions with sclerosis within vertebral bodies suggestive of osteomalacia/diffuse infiltrative disorder. The free light chain (FLC) assay revealed increment in the free kappa light chain and an abnormal  $\kappa/\lambda$  ratio. Free Light Chain assay (FLC) when used in complement with Protein Electrophoresis (PEP) and Immunofixation Electrophoresis (IFE) were pivotal in diagnosis of non-secretory multiple myeloma or light chain myelomas. FLC is a useful monitoring tool because it reflects therapy results due to short serum half-life.

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