Ann Hematol (2014) 93:1201–1206
DOI 10.1007/s00277-014-2019-y

ORIGINAL ARTICLE

Serum immunoglobulin free light chain and heavy/light chain measurements in POEMS syndrome

Chen Wang · Wei Su · Wei Zhang · Qian Di · Ming-Hui Duan · Wei Ji · Xin-Xin Cao · Dao-Bin Zhou · Jian Li

Received: 14 November 2013 / Accepted: 14 January 2014 / Published online: 31 January 2014

Abstract POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome is a rare plasma cell dyscrasia. Nearly all patients present with a λ-restricted monoclonal gammopathy. Most patients with POEMS syndrome have been reported to have a normal serum free light chain ratio (sFLC-R), but the underlying mechanism is still unclear. We assessed the serum free light chains in 83 patients with newly diagnosed POEMS syndrome. The clinical and laboratory data associated with this disorder were collected to identify factors affecting sFLC-R. Fifty-six patients (67 %) showed elevated serum free λ light chains, but only 11 patients (13 %) had an abnormal sFLC-R. A comparison of patients with and without abnormal sFLC-Rs indicated that the latter group had more common splenomegaly and worse renal function. However, the introduction of an extended renal range for sFLC-R did not dramatically improve the diagnostic value of sFLC-R in these patients. Further analyses identified a correlation between the serum free κ light chain and the uninvolved immunoglobulin in patients with an IgAλ clone, implying that the activation of polyclonal immunoglobulin production could mask the presumed skewing of the sFLC-R induced by the underlying monoclonal gammopathy. Therefore, a serum heavy/light chain (sHLC) assay was performed in a subset of patients with stored serum samples available, and the prevalence of abnormal sHLC ratios was high in these patients. In summary, the overproduction of polyclonal immunoglobulin accounts for the high frequency of normal sFLC-R in patients with POEMS syndrome. The sHLC assay may provide unique information about this disorder.

Keywords POEMS syndrome · Free light chain · Heavy/light chain · Involved immunoglobulin · Uninvolved immunoglobulin

Introduction

POEMS syndrome is a rare paraneoplastic syndrome, involving polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes [1–3]. Other important clinical manifestations include osteosclerosis, Castleman's disease, extravascular volume overload, papilledema, and pulmonary disease. The vast majority of patients present with a λ-restricted plasma cell disorder [1]. The underlying mechanism of this syndrome is not well understood. Elevated vascular endothelial growth factor (VEGF) occurs in most patients and correlates best with disease activity [4, 5], although it may not be the driving force of this disorder because the results of anti-VEGF therapy are mixed [6–8].

Monoclonal plasma cell disorders can produce abnormal concentrations of serum free κ or λ light chains, resulting in an abnormal serum free light chain ratio (sFLC-R), which also reflects the clonality of the disease [9]. The test developed by Bradwell and colleagues in 2001 is the most specific and sensitive test for the quantitation of sFLC, with good precision [10]. This test is particularly useful in the diagnosis and

Chen Wang and Wei Su contributed equally to this work.

Electronic supplementary material The online version of this article (doi:10.1007/s00277-014-2019-y) contains supplementary material, which is available to authorized users.

C. Wang · W. Zhang · M.-H. Duan · X.-X. Cao · D.-B. Zhou · J. Li (✉)
Department of Hematology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China
e-mail: lijian@pumch.cn

W. Su · Q. Di · W. Ji
Department of Clinical Laboratory, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

management of light chain diseases and has been incorporated into the international guidelines for clinical decisions regarding multiple myeloma and amyloid light-chain (AL) amyloidosis [11, 12].

Because an abnormal sFLC-R is always detected in patients with plasma cell disorders, ranging from one third in monoclonal gammopathy with undetermined significance (MGUS) to most in multiple myeloma or primary amyloidosis (AL), we thought that this might also be true for POEMS syndrome. A recent study indicated that only 18 % of patients with POEMS syndrome had abnormal sFLC-Rs, although most had elevated serum free λ light chains [13]. The cause of the normal sFLC-R in these patients seems to be multifactorial, and the precise mechanism is still unclear. Here, we assessed the sFLC levels in patients with POEMS syndrome and explored the reasons for our observations.

Methods

Patients

Of 263 patients with POEMS syndrome who were seen at Peking Union Medical College Hospital (PUMCH) between January 2002 and June 2013, 83 patients were included in this study because a serum FLC assay was performed as part of their clinical workup. These patients were referred to our hospital from more than 30 centers throughout the country, and all met the diagnostic criteria proposed by Dispenzieri: (1) presence of both polyneuropathy and monoclonal gammopathy; (2) presence of one of the following three major criteria: Castleman's disease, osteosclerosis, or elevated VEGF; and (3) one of the six minor criteria: organomegaly, extravascular volume overload, endocrinopathy, skin changes, papilledema, and either thrombocytosis or polycythemia [2]. All patients gave their informed consent, and the study was approved by the Institutional Review Board of PUMCH.

The detailed clinical features of POEMS syndrome patients were recorded at the time of diagnosis. In particular, the Overall Neuropathy Limitation Scale (ONLS) score was used to assess neurological disability, as described previously [14]. Organomegalies, including hepatomegaly, splenomegaly, and lymphadenopathy, were evaluated with physical examination, ultrasonography, and/or computed tomography (CT) scan. Laboratory data associated with POEMS syndrome were collected, including bone marrow aspiration, serum immunoglobulin level, and serum and urine immunofixation. Serum levels of immunoglobulin (IgG, IgM, and IgA) were determined by nephelometry (DiaSys Diagnostic Systems, Germany) with the automatic biochemistry analyzer AU5800 (Beckman Coulter, USA). Serum VEGF was measured with an enzyme-linked immunosorbent assay (ELISA), as described elsewhere (normal range of <600 pg/mL) [14]. Serum creatinine levels were measured with an enzymatic method using the Roche Diagnostics Modular Analytics analyzer. The normal range was 45–84 μmol/L for females and 59–104 μmol/L for males. The estimated glomerular filtration rate (eGFR) was calculated using the abbreviated modification of diet in renal disease (MDRD) equation [15]. The characteristics of these 83 patients were not different from the entire patient cohort seen at our hospital (Supplementary Table).

Serum FLC and heavy/light chain assays

The serum FLC assay (Freelite, Binding Site, Birmingham, UK) was performed on a Dade Behring BN II Nephelometer with the following reference ranges: κ, 3.3–19.4 mg/L, and λ, 5.7–26.3 mg/L [16]. The test results allowed the calculation of the serum κ/λ free light chain ratio (sFLC-R; normal range 0.26–1.65) [16]. Recently, an expanded reference range for the sFLC-R (0.37–3.1) was introduced for patients with renal impairment [17].

The serum immunoglobulin heavy/light chain (HLC) pairs (IgAκ/IgAλ and IgGκ/IgGλ) were assessed using the Hevylite kit (Binding Site, Birmingham, UK) on a Dade Behring BN II Nephelometer [18]. Ten patients for whom serum samples were collected and stored within 30 days of their presentation at our hospital were tested. sHLC ratios outside the normal ranges (IgAκ/IgAλ, 0.7–2.2; IgGκ/IgGλ, 1.3–3.7) were considered to indicate monoclonal gammopathy [19].

Statistical analyses

All analyses were performed with SPSS 17 (SPSS, Inc., Chicago, IL, USA). The Mann–Whitney *U* test or Student's *t* test was used to analyze the differences in continuous variables between groups. Fisher's exact test was used to analyze differences in categorical variables between groups. Spearman's rho was used to measure the linear relationship between two variables. For all analyses, a two-tailed *p* value of less than 0.05 was considered statistically significant.

Results

Clinical and laboratory characteristics of the study population

The clinical and laboratory data for the patients at presentation are summarized (Table 1). Of the 83 patients examined, 63 % were male. The median age was 46 years (range 24–68 years). All the patients had polyneuropathy with a median ONLS score of 4.5 (range 0–12) and a λ-restricted plasma cell disorder. In the serum analysis, 53 patients had monoclonal IgAλ, 24 patients had monoclonal IgGλ, and 1 patient had monoclonal IgDλ. Two patients were biclonal (one had IgAλ and IgGλ; the other had IgAλ and IgDλ), and three patients only

Table 1 Patients' characteristics and comparison of patients with and without abnormal FLC-R

	All patients	Abnormal FLC-R	Normal FLC-R	*p* value
	N=83	*N*=11	*N*=72	
Age, median (range)	46 (24–68)	48 (27–63)	45 (24–68)	
Sex (male, %)	63	73	61	
Ig heavy chain isotype				
IgA/IgG/IgD/biclonal/none	53/24/1/2/3			
IgA (%)		55	65	
None (%)		27	0	<0.001
BMPC, median (range) (%)	1.5 (0–17.5)	2 (0–17.5)	1.5 (0–14)	
Serum VEGF (pg/mL)	3,138 (420–22,993) (*N*=77)	3,865	3,079 (*N*=66)	
Serum creatinine (μmol/L)	76 (30–345) (*N*=82)	65 (31–103)	77 (30–345) (*N*=71)	0.036
eGFR (MDRD) (mL/min/1.73 m^2)	97.9 (16.0–301.7) (*N*=82)	133.9 (51.7–224.7)	92.6 (16.0–301.7) (*N*=71)	0.012
Immunoglobulin (g/L)	*N*=63	*N*=9	*N*=54	
IgG	11.1 (5.1–30)	8.45 (5.8–13.2)	11.35 (5.1–30)	
IgA	3.06 (0.67–10.96)	3.52 (0.8–10.96)	2.93 (0.67–7.04)	
IgM	1.16 (0.44–2.7)	0.86 (0.68–2.63)	1.19 (0.44–2.7)	
Serum κ FLC (mg/dL)	19.5 (6.0–146.2)	11.4 (7.1–27.1)	20.4 (6.0–146.2)	
Serum λ FLC (mg/dL)	44.8 (7.3–520.0)	88.4 (37.7–520)	37.7 (7.3–237.9)	0.001
Serum κ/λ FLC-R	0.54 (0.03–1.12)	0.12 (0.03–0.19)	0.57 (0.29–1.12)	<0.001

ONLS Overall Neuropathy Limitation Scale, *VEGF* vascular endothelial growth factor, *BMPC* bone marrow plasma cells, *MDRD* modification of diet in renal disease, *Ig* immunoglobulin, *FLC* free light chain, *FLC-R* free light chain ratio

had a detectable monoclonal λ light chain. The majority of patients displayed organomegaly (95 %), endocrinopathy (80 %), skin changes (96 %), and extravascular volume overload (88 %); 41 patients (49 %) had sclerotic bone lesions; and 9 (11 %) had coexistent Castleman's disease. Serum VEGF levels were dramatically elevated in nearly all the patients.

The serum free λ light chain was elevated in 56 patients (67 %; median 44.8 mg/L, range 7.3–520 mg/L). The uninvolved serum free light chain, herein the serum κ light chain (median 19.5 mg/L, range 6.0–146.2 mg/L), was elevated in 51 % of patients. The results of the serum free light chain assay allowed us to calculate the sFLC-R (median 0.54, range 0.03–1.12). In summary, only 13 % of patients had an abnormal sFLC-R.

Comparison of patients with and without abnormal sFLC-R

The clinical and laboratory features of the patients with and without abnormal sFLC-R were compared. Splenomegaly was less frequently detected in patients with an abnormal sFLC-R (45 vs 76 %, $p=0.033$). All three patients with only monoclonal λ light chain had an abnormal sFLC-R and were classified in the abnormal sFLC-R group. Serum free λ light chain was elevated more obviously in the abnormal sFLC-R group (88.4 vs 37.7 mg/L, $p=0.001$). Patients with an abnormal sFLC-R had lower serum creatinine levels (65 vs 77 μmol/L, $p=0.036$) and higher eGFR (133.89 vs 92.55 mL/min/1.73 m^2, $p=0.012$). There were no differences between the two groups in age, sex distribution, other key clinical features of POEMS syndrome, bone marrow plasma cell percentage, serum free κ light chain, serum VEGF, or serum immunoglobulin levels.

Extended renal reference range for sFLC-R in patients with POEMS syndrome

The sFLC-Rs were further analyzed in the context of renal function. An extended renal reference range for sFLC-R (0.37–3.1), which was developed for patients with renal insufficiency, was used. When serum creatinine levels were used to evaluate the renal function of patients with normal sFLC-Rs, only one of them with renal dysfunction had a sFLC-R within the interval between the lower limits of the original and extended ranges of FLC-R (0.26–0.37), which could be considered abnormal. Because serum creatinine is a less reliable index of renal function, the eGFRs of these patients were calculated. Thirty-five patients (48 %) had renal insufficiency, which could have been considered as a chronic kidney disease (eGFR of <90 mL/min/1.73 m^2), but only four of them had an abnormal sFLC-R when the extended interval for FLC-R was used. As a result, only 18 % of the patients had an abnormal sFLC-R with the use of the extended renal range.

Overproduction of uninvolved immunoglobulins in patients with normal FLC-R

As activated polyclonal immunoglobulin production may mask the underlying clonal disorders, we next assessed whether this is true for patients with POEMS syndrome. Because the uninvolved immunoglobulin is definitely polyclonal in patients with clonal gammopathy, a correlation analysis was performed in IgAλ patients whose serum immunoglobulin levels were available (n=36). As shown in Fig. 1, there was a fair, statistically significant correlation between the serum free κ light chain and the uninvolved immunoglobulin (IgG and IgM) (rho 0.515, p=0.001). Further analysis showed a good linear relationship between the serum free κ and λ light chains (rho 0.934, p<0.001). However, no such correlation was observed in IgGλ patients whose serum immunoglobulin data were available (n=16).

HLC measurements in patients with POEMS syndrome

To avoid the influence of uninvolved immunoglobulin, we performed the newly developed HLC assay, which can measure the levels of isotype-specific immunoglobulin (such as IgAκ and IgAλ in IgAλ patients), in 10 patients with serum samples stored at the time of presentation. In the IgAλ patients, 80 % had elevated IgAλ levels (median 1.81 g/L, range 1.17–9.89 g/L), and 20 % had uninvolved immunoglobulin (IgAκ) suppression (median 0.84 g/L, range 0.37–1.23 g/L). Eighty percent of the IgAλ patients had an abnormal IgAκ/IgAλ ratio (median 0.32, range 0.04–1.01). In the IgGλ patients, the levels of affected light chain-specific immunoglobulin (IgGλ) (median 6.68 g/L, range 2.94–20.3 g/L) were elevated in 80 % of patients, and the IgGκ levels (median 6.34 g/L, range 3.57–9.6 g/L) were suppressed in 20 % of patients. All IgGλ patients showed abnormal IgGκ/IgGλ ratios (median 1.1, range 0.31–1.21).

Discussion

In this study, we found that serum FLC-Rs were normal in 87 % of patients with POEMS syndrome, although all of them had documented λ-restricted monoclonal gammopathy. This finding was unexpected, because the sFLC-R is thought to be a diagnostic marker for multiple myeloma and AL amyloidosis.

To determine the reasons for this unexpected finding, we first compared the clinical and laboratory features of patients with and without abnormal sFLC-Rs and found more common splenomegaly and renal insufficiency in the latter group. If we consider the catabolism of the free light chain, these findings are reasonable. Normally, the sFLC-R is determined by the slower renal clearance of dimeric λ light chain, causing the median ratio to be about 0.58, although approximately

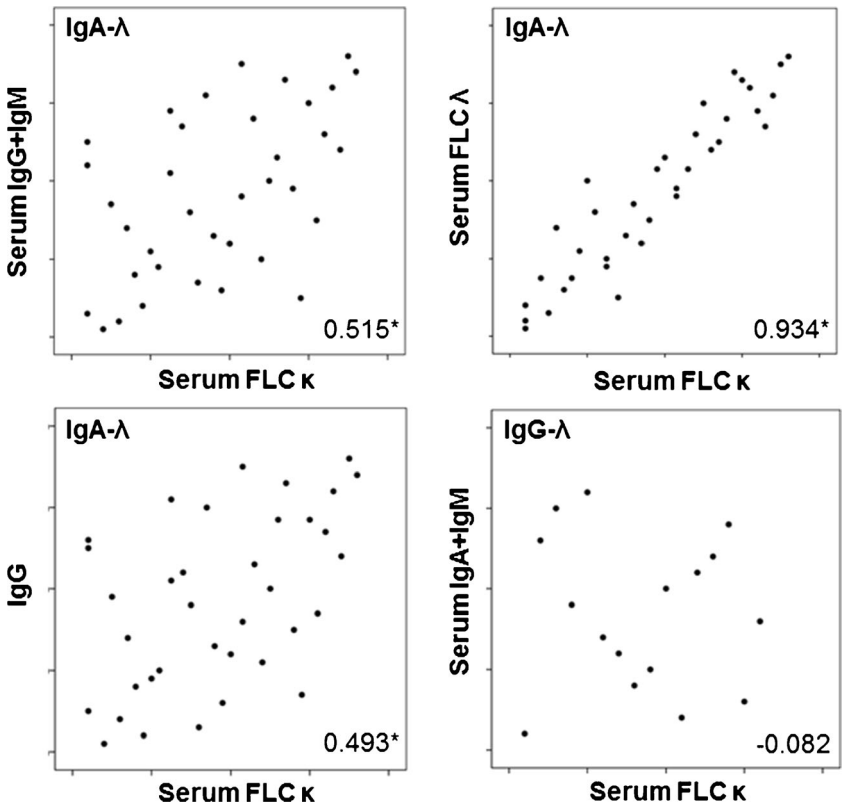

Fig. 1 Relationships between serum free light chain (*FLC*) and serum immunoglobulin (*Ig*) in IgAλ and IgGλ patients. The uninvolved immunoglobulin was used to represent the polyclonal immunoglobulin. For patients with IgAλ clone, the uninvolved immunoglobulins indicate IgA and IgM. Likewise, the uninvolved immunoglobulins in IgGλ patients are IgA and IgM. The data were analyzed with Spearman's rho, and *the numbers in each of the boxes* are Spearman's rho correlation coefficients. *p<0.05

twice as much κ light chain is produced as λ light chain [16, 20]. With renal insufficiency, the serum κ and λ light chains are eliminated equally via pinocytosis by the reticuloendothelial system, which is not dependent on the molecular weight [9]. Therefore, in patients with advanced renal disease, the median value for sFLC-R is 1.19 [17]. POEMS syndrome patients with normal sFLC-Rs showed more obvious renal insufficiency, which could influence the renal excretion of the serum free light chains. Moreover, these patients also had a higher frequency of splenomegaly, which might be considered as a clinical surrogate for the active reticuloendothelial system. As a result, the sFLC-R might be misinterpreted in these patients, because of the shift of normal range.

These considerations prompted us to analyze the sFLC-R in the context of renal function. An extended renal reference range for sFLC-R has been established using data from patients with chronic kidney disease [17] and has shown improved diagnostic accuracy for multiple myeloma patients with renal insufficiency [21]. When we used this reference range, the percentage of patients with abnormal sFLC-Rs increased from 13 to 18 %, indicating that renal impairment might not be the main reason for a normal sFLC-R.

Splenomegaly is more frequently detected in patients with normal sFLC-Rs. The pathogenesis of this manifestation in POEMS syndrome is unclear. Traditional views attribute it to increased permeability [2], which may lead to active reticuloendothelial function, as aforementioned. Another reasonable explanation is that there are expansions of polyclonal plasma cells in tissues normally harboring B cells, i.e., the spleen [13]. This hypothesis is attractive, as polyclonal plasma cells produce serum free κ and λ light chains proportionately, resulting in a normal sFLC-R. Several other clues in POEMS syndrome also support this hypothesis, including the markedly elevated proinflammatory cytokines in the serum and the coexisted reactive plasma cells with the clonal ones in the bone marrow [22, 23]. Thus, we postulated that the discordance between the normal sFLC-R and the underlying λ-restricted monoclonal gammopathy might be explained by the overproduction of polyclonal immunoglobulin, and this appeared to be the case. We used the uninvolved immunoglobulin to represent the polyclonal fraction and found a linear correlation between it (herein, IgG+IgM) and the serum free κ light chain in IgAλ patients, in which IgG was the main contributor. This finding indicates that the elevated serum free κ light chain, which disrupted the presumed skewing of sFLC-R induced by λ-restricted monoclonal gammopathy, was actually associated with polyclonal immunoglobulin production. However, in IgGλ patients, no such correlation was observed. This is not surprising, since IgG is the main constituent of polyclonal immunoglobulin and could reflect this fraction in IgAλ patients. However, in IgGλ patients, the uninvolved immunoglobulin (IgA and IgM) could not reflect the polyclonal immunoglobulin well. As a result, although serum free κ light chain is thought to be polyclonal, it only showed a correlation with the uninvolved immunoglobulin in IgAλ patients.

The newly developed serum HLC assay allowed us to accurately measure the serum levels of isotype-specific immunoglobulin, avoiding the influence of overproduced uninvolved immunoglobulin and permitting the calculation of light chain-specific immunoglobulin ratio of the disease isotype (e.g., IgAκ/IgAλ in IgAλ patients) [18]. To our knowledge, this study is the first one to measure sHLC in patients with POEMS syndrome, although the preliminary result was limited by the small number of patients (12 %). As expected, abnormal sHLC ratios were observed in nearly all patients and could reflect their disease clonality. This finding implies that result of HLC assay may have potential values to deepen our knowledge of POEMS syndrome.

In summary, we have made several valuable observations with relevance for the clinical practice of POEMS syndrome. Actively produced polyclonal immunoglobulin with free light chains interrupts the skewing of the sFLC-R induced by the underlying monoclonal gammopathy, making sFLC assay not useful in the diagnosis and follow-up of patients with POEMS syndrome, in contrast to its clinical value for multiple myeloma and AL amyloidosis. Meanwhile, serum and urine immunofixation still remained as the gold standard to detect the monoclonal gammopathy in POEMS syndrome. Moreover, the sHLC assay may provide additional information, especially for IgAλ patients, although extensive studies in large cohorts are still required.

Acknowledgments The authors thank all the patients who participated in this study. The authors would like to extend their appreciation to Mr. Hao Cai and Ms. Xuan Wang for their technical assistance and to Ms. Tianjiao Li for her maintenance of the serum sample collection of patients with POEMS syndrome. This study was funded by the Capital Health Research and Development of Special (no. 2011-4001-03), Beijing Municipal Science & Technology Commission (no. Z111107058811019), Peking Union Medical College New Star (2011, for LJ), and National Public Health Grand Research Foundation (no. 201202017).

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Dispenzieri A, Kyle RA, Lacy MQ et al (2003) POEMS syndrome: definitions and long-term outcome. Blood 101(7):2496–2506
2. Dispenzieri A (2011) POEMS syndrome: 2011 update on diagnosis, risk-stratification, and management. Am J Hematol 86(7):591–601
3. Li J, Zhou DB (2013) New advances in the diagnosis and treatment of POEMS syndrome. Br J Haematol 161(3):303–315
4. Watanabe O, Arimura K, Kitajima I et al (1996) Greatly raised vascular endothelial growth factor (VEGF) in POEMS syndrome. Lancet 347(9002):702
5. Watanabe O, Maruyama I, Arimura K et al (1998) Overproduction of vascular endothelial growth factor/vascular permeability factor is

causative in Crow-Fukase (POEMS) syndrome. Muscle Nerve 21(11):1390–1397
6. Badros A, Porter N, Zimrin A (2005) Bevacizumab therapy for POEMS syndrome. Blood 106(3):1135
7. Samaras P, Bauer S, Stenner-Liewen F et al (2007) Treatment of POEMS syndrome with bevacizumab. Haematologica 92(10):1438–1439
8. Kanai K, Kuwabara S, Misawa S, Hattori T (2007) Failure of treatment with anti-VEGF monoclonal antibody for long-standing POEMS syndrome. Intern Med 46(6):311–313
9. Davids MS, Murali MR, Kuter DJ (2010) Serum free light chain analysis. Am J Hematol 85(10):787–790
10. Bradwell AR, Carr-Smith HD, Mead GP et al (2001) Highly sensitive, automated immunoassay for immunoglobulin free light chains in serum and urine. Clin Chem 47(4):673–680
11. Dispenzieri A, Kyle R, Merlini G et al (2009) International Myeloma Working Group guidelines for serum-free light chain analysis in multiple myeloma and related disorders. Leukemia 23(2):215–224
12. Gertz MA (2013) Immunoglobulin light chain amyloidosis: 2013 update on diagnosis, prognosis, and treatment. Am J Hematol 88(5):416–425
13. Stankowski-Drengler T, Gertz MA, Katzmann JA et al (2010) Serum immunoglobulin free light chain measurements and heavy chain isotype usage provide insight into disease biology in patients with POEMS syndrome. Am J Hematol 85(6):431–434
14. Li J, Zhang W, Jiao L et al (2011) Combination of melphalan and dexamethasone for patients with newly diagnosed POEMS syndrome. Blood 117(24):6445–6449
15. Levey AS, Bosch JP, Lewis JB et al (1999) A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 130(6):461–470
16. Katzmann JA, Clark RJ, Abraham RS et al (2002) Serum reference intervals and diagnostic ranges for free kappa and free lambda immunoglobulin light chains: relative sensitivity for detection of monoclonal light chains. Clin Chem 48(9):1437–1444
17. Hutchison CA, Harding S, Hewins P et al (2008) Quantitative assessment of serum and urinary polyclonal free light chains in patients with chronic kidney disease. Clin J Am Soc Nephrol 3(6):1684–1690
18. Bradwell AR, Harding SJ, Fourrier NJ et al (2009) Assessment of monoclonal gammopathies by nephelometric measurement of individual immunoglobulin kappa/lambda ratios. Clin Chem 55(9): 1646–1655
19. Katzmann JA, Clark R, Kyle RA et al (2013) Suppression of uninvolved immunoglobulins defined by heavy/light chain pair suppression is a risk factor for progression of MGUS. Leukemia 27(1):208–212
20. Drayson M, Tang LX, Drew R et al (2001) Serum free light-chain measurements for identifying and monitoring patients with nonsecretory multiple myeloma. Blood 97(9):2900–2902
21. Park JW, Kim YK, Bae EH et al (2012) Combined analysis using extended renal reference range of serum free light chain ratio and serum protein electrophoresis improves the diagnostic accuracy of multiple myeloma in renal insufficiency. Clin Biochem 45(10–11): 740–744
22. Gherardi RK, Bélec L, Soubrier M et al (1996) Overproduction of proinflammatory cytokines imbalanced by their antagonists in POEMS syndrome. Blood 87(4):1458–1465
23. Dao LN, Hanson CA, Dispenzieri A et al (2011) Bone marrow histopathology in POEMS syndrome: a distinctive combination of plasma cell, lymphoid, and myeloid findings in 87 patients. Blood 117(24):6438–6444