ORIGINAL PAPERS

Adv Clin Exp Med 2014, **23**, 4, 531–538
ISSN 1899–5276

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Analysis of Free Serum Light Chains in Patients Suffering from Multiple Myeloma Complicated by Light-Chain Amyloidosis

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article; **G** – other

Abstract

Background. AL amyloidosis is an acquired systemic disease in which a pathologic amorphous substance produced as a result of abnormal protein metabolism is deposited in the extracellular space of various tissues.
Objectives. The aim of the study was to investigate the relationship between the kappa and lambda serum free light chains (sFLCs) and the development of AL amyloidosis in patients suffering from multiple myeloma (MM).
Material and Methods. The investigations included 70 MM patients, 40 females and 30 males, aged 28–83 years. In 37 persons, MM was had been diagnosed recently; 33 patients had been undergoing treatment. Amyloidosis was diagnosed in 18 patients (25.7%), including nine females, nine males; six had newly diagnosed disease. Fifteen patients developed kidney failure. The control group consisted of 10 healthy donors. The concentration of sFLC ls were determined using the immunonephelometric method and expressed in mg/L.
Results. In 18 MM patients with amyloidosis the concentration of κ sFLCs ranged from 0.3 to 4780 (x = 854.5, SD = 1289), and was significantly higher (p = 0.039) than in the group without amyloidosis, where the range was from 0.3 to 426.0 (x = 68.9, SD = 98.1). The highest concentration of κ sFLCs was observed in the group of five patients with amyloidosis and renal failure. The concentration of λ sFLCs in patients with amyloidosis ranged from 0.5 to 41600 (x = 3035.7, SD = 9735) and was higher than in MM patients without amyloidosis, where it ranged from 0.5 to 834.0 (x = 79.3, SD = 193). In amyloidosis patients, the concentration of λ sFLCs was significantly higher (p = 0.05) in cases of renal failure as compared with the patients with normal renal function.
Conclusions. The concentration of sFLCs is a strong indicator of amyloidosis development in MM patients (**Adv Clin Exp Med 2014, 23, 4, 531–538**).

Key words: multiple myeloma, amyloidosis, kappa and lambda serum free light chains.

Amyloidosis is an inherited or acquired systemic storage disease in which a pathologic, amorphous substance produced as a result of abnormal protein metabolism and resistant to proteolysis is deposited in the extracellular space of various tissues. It leads to the destruction of normal tissue structure and disturbs its function. The disease may affect one organ or several organs simultaneously, and is always fatal [1–3]. In light-chain amyloidosis (AL amyloidosis, or AL), the amyloid deposits consist of monoclonal immunoglobulin light chains, which are the product of neoplastic plasma cell clones. Depending on the number of plasma cells in the bone marrow, the serum and/or urine level of monoclonal protein, as well as the presence of osteolytic changes, it is possible to diagnose AL, or AL in the course of myeloma (and other monoclonal gammopathies). Kyle and Gertz

demonstrated that 85% of all patients diagnosed with AL amyloidosis meet the criteria of various forms of plasma cell dyscrasias, while the remaining 15% lack clinical symptoms of clonal growth of plasma cells [2]. According to Abraham et al., all patients with AL amyloidosis reveal monoclonal gammopathy on the basis of evaluations of their serum free light chain levels [4]. AL amyloidosis affects organs originating from the mesoderm tissue (the heart, digestive tract, peripheral nervous system, skin and tongue).

In normal conditions, serum free light chains (sFLCs) are produced in the amount of approximately 0.5–1.0 g/day and their half-life depends on kidney function.

Serum FLCs are filtered in the kidney glomeruli and metabolized in nephron proximal tubules, in amounts as high as 10–30g of sFLCs/24 hours, which means that even at very high concentrations, sFLC excretion with urine may be small. This suggests that FLC concentration in serum and not in urine is a disease indicator in plasma cell dyscrasias [5, 6].

The first examination of sFLCs in AL amyloidosis was carried out in 2002 at the National Amyloidosis Center in London [7]. In 262 out 265 patients (98%), the presence of sFLCs was detected in the course of the disease. In another study carried on 110 AL amyloidosis patients, Katzmann et al. demonstrated that in serum, immunofixation proved positive in 68% of the cases; in urine in 83%; and in a nephelometric test the κ/λ ratio exceeded the normal range in 91% of the cases [8]. Other authors' studies have confirmed immunoephelometric test sensitivity in 68–86% of patients in whom both immunofixation and electrophoresis proved negative [9].

The goal of this study was to investigate the relationship between kappa and lambda sFLCs, as well as the development of AL amyloidosis in patients suffering from multiple myeloma (MM).

Material and Methods

Patients

The study was approved by the Bioethical Committee of Wroclaw Medical University (Wroclaw, Poland). It included 70 MM patients, 40 females and 30 males, aged 28–83 years. In 37 patients, MM was had been diagnosed recently, while 33 patients had been undergoing treatment for 2 to 34 months. Kidney failure had developed in 15 patients. Diagnoses of MM and solitary plasmocytoma were based on standard criteria (Table 1).

The diagnosis of amyloidosis was based on the presence of green-colored amyloid deposits under polarized light microscope in the adipose tissue harvested from the abdominal fold. Amyloidosis was diagnosed in 18 patients (25.7%), nine males and nine females, six of whom had been newly diagnosed MM and 12 in whom the disease had progressed or recurred; their ages were from 47 to 83 years (x = 63.5 years, SD = 9.4). In 52 of the MM patients (74.3%), including 31 females aged 28–81 years, (x = 61.8 years, SD = 11.7), amyloidosis was not detected. Amyloidosis was not diagnosed in any patient suffering from solitary plasmocytoma, and due to the small number of these patients, they were included in the non-amyloid MM group.

Table 1. Selected clinical and laboratory data of the patients in the study

Number	70
Age (years, median, range)	x = 61.1; SD = 11.1; range: 28–83
Sex F/M	40/30
Newly diagnosed disease/disease progression	37/33
Multiple Myeloma	
IgG/IgA/IgM/LCD (light chains disease)	34/16/4/6
Non-secretory MM	6
Other (solitary MM)	4
Light chain type K/L	45/19
Clinical stage	
IA/IIA/IIB/IIIA/IIIB/not defined	1/22/3/27/12/5
Kidney function A/B	55/15
Amyloidosis Y/N	18/52
Overall survival (OS) median (months)	40

The control group consisted of 10 volunteer donors, five females and five males**,** aged 19–32 years (x = 22.5; SD = 4.4).

An adipose tissue biopsy was performed on all patients. The aspirated material was mottled on a slide and after drying for one hour it was stained with Congo red and subsequently assessed under a polarized light microscope (Fig. 1).

The determination of the sFLC concentration was performed by the immunonephelometric method using Freelite Human Kappa and Lambda Free kits (The Binding Site) applied in a *Dade Behring BN II Nephelometer (Simens)* and expressed in mg/L.

Fig. 1. Amyloid deposits stained with Congo red under polarizing light microscope in a multiple myeloma patient

Freelite Human Kappa and Lambda Free kits are designed to determine sFLC concentration in the range 5.9–190 mg/L at a dilution of 1 : 100. At a sample dilution of 1 : 8000, concentrations up to 15.200 mg/L can be determined. The referential value for free human kappa light chains (KF) is 3.300 to 19.400 mg/L; for free human lambda light chains (LF) it is 5.710 to 26.300 mg/L; and for the kappa/ /lambda ratio the referential value is 0.260 to 1.650.

Results

Analysis of κ sFLC Concentrations in MM Patients

Concentrations of κ sFLCs in MM patients ranged from 0.3 to 4780.0 (x = 271, SD = 732) and was significantly higher (p = 0.0463) than the concentration of these chains in the controls, (range: 3.8 – 19.1, x = 13, SD = 6.5) (Fig. 2). The concentration of κ sFLCs in newly diagnosed patients ranged from 0.32 to 4780.0 (x = 253.0, SD = 802.0) and did not differ significantly from the value found in the patients who had already been treated, where it varied from 0.27 to 2670.0 (x = 291 SD = 658). The concentration of κ sFLCs in the 15 patients with renal failure ranged from 0.3 to 4780 (x = 336, SD = 816) and was significantly higher (p = 0.01) than the concentration found in the 55 patients with normal renal function (range: 13–113, x = 32, SD = 35.7).

Analysis of κ sFLC Concentrations in MM Patients with Amyloidosis

Concentrations of κ sFLCs of the 18 MM patients with amyloidosis ranged from 0.3 to 4780 (x = 854.5, SD = 1289) and were significantly higher (p = 0.039) than in the group without AL, where the concentrations ranged from 0.3 to 426 (x = 68.9, SD = 98.1) (Fig. 3).

The highest concentration of κ sFLCs was observed in the group of five MM patients with amyloidosis and renal failure. It was significantly higher (p = 0.0008) than in renal dysfunction group without amyloidosis; the ranges were 0.27–4780 (x = 1176, SD = 1398) and 0.27–426 (x = 76, SD = 108), respectively. It was also significantly higher (p = 0.001) in comparison with amyloidosis patients with normal renal function (1.33–113, x = 38.5, SD = 36.8). The lowest concentration of κ sFLCs was found in patients without amyloidosis or renal failure.

Amyloidosis occurred in 12 out of 45 dominant κ light chain MM patients and significantly more

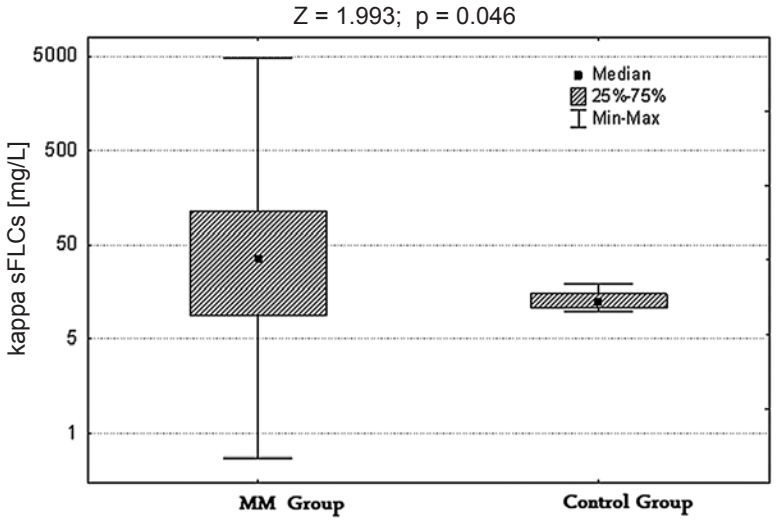

Fig. 2. Concentration of κ sFLCs in MM patients and in controls

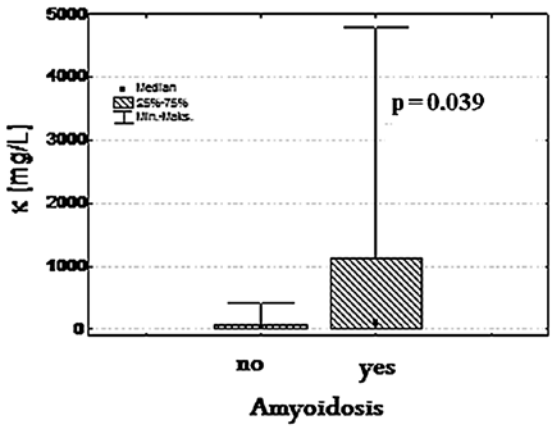

Fig. 3. Concentration of κ sFLCs in MM patients with and without amyloidosis

often in kappa IgG myeloma, (9/10 patients) than in kappa IgA patients (1/3 patients) (p = 0.05).

For the cut-off value κ > 426 mg/L, sensitivity amounted to 44.4%, specificity to 100% and the area under the ROC curve (AUC) was 0.664 (Fig. 4).

For the cut-off value κ > 94.7 mg/L, sensitivity amounted to 50.0% and specificity to 80.8%. For this cut-off value, the odds ratio (OR) was 4.2 and the 95% confidence range extended from 1.33 to 13.30. This means that the probability of amyloidosis occurrence in MM patients with κ sFLCs > > 95 mg/L was over four times higher than in patients with lower κ sFLC values. This difference was statistically significant (p = 0.05).

In the group of amyloidosis MM patients, the concentration of κ sFLCs revealed positive correlations with lactate dehydrogenase (*LDH)* concentration in serum (r = + 0.2740, p = 0.003) and with beta2-m concentrations in serum (r = + 0.3747, p = 0.03).

Analysis of λ sFLCs Concentrations in MM Patients

Concentrations of λ sFLCs in MM patients varied from 0.51 to 41600 (x = 839, SD = 5007) and were higher than the concentrations of λ chains in the healthy controls (range 5.7–23.4, x = 14.3, SD = = 5.9; p = 0.120) (Fig. 5). Concentrations of λ sFLCs in newly diagnosed patients did not differ significantly from the values observed in those who had already been treated. Concentrations of λ sFLCs in the 15 renal failure patients ranged from 0.5 to 41600 (x = 3434, SD = 10649) and were significantly higher than in the group with normal renal function (range: 0.5–3210, x = 132, SD = 507; p = 0.0037).

Analysis of λ sFLCs Concentrations in MM Patients with Amyloidosis

Concentrations of λ sFLCs in the 18 MM patients with amyloidosis ranged from 0.5 to 41600 (x = 3035.7, SD = 9735); in the MM group without amyloidosis the range was 0.5–834, (x = 79.3, SD = 193). The difference was not statistically significant, probably due to the high values of standard deviation (Fig. 6).

Concentrations of λ sFLCs in MM patients with amyloidosis, with and without renal failure, were significantly higher (p = 0.05 and p = 0.04 respectively) than in the group with no amyloidosis, regardless of renal function. In amyloidosis patients, λ sFLCs concentrations were significantly higher (p = 0.05) in the case of renal failure as compared with patients with a normal creatinine concentration.

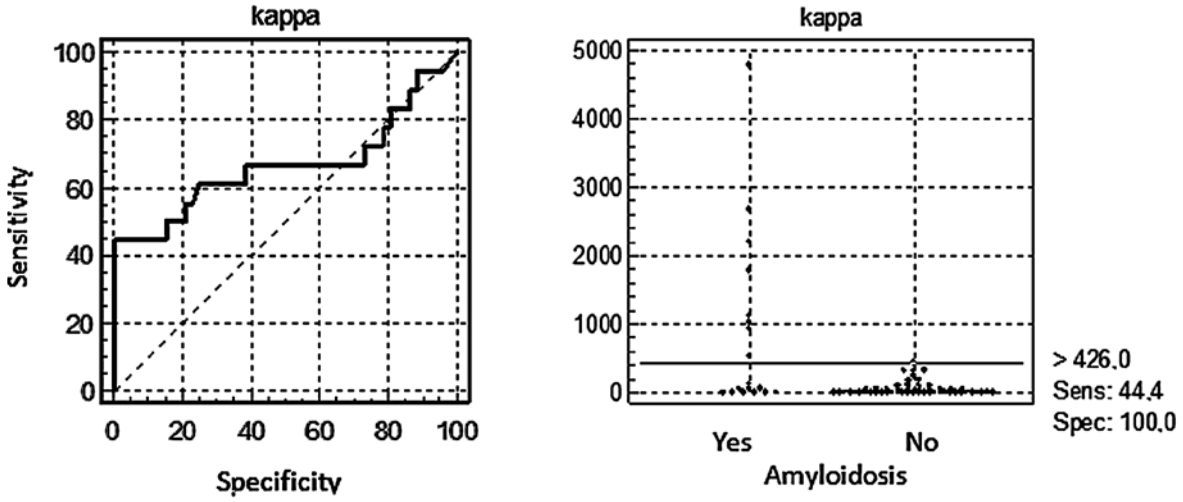

Fig. 4. ROC curve for κ light chains in 70 MM patients

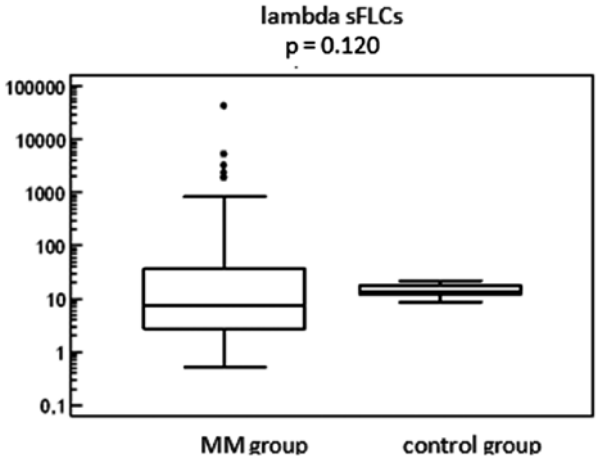

Fig. 5. Concentration of λ sFLCs in MM patients and in controls

Amyloidosis occurred in six out of 19 MM patients in whom the lambda light chain was detected. No type of lambda chain myeloma proved dominant in amyloidosis development.

For cut-off value λ > 843 mg/L, sensitivity amounted to 27.8%, specificity was 100%, and the area under the ROC curve (AUC) was 0.567 (Fig. 7). For cut-off value λ > 6.4 mg/L, sensitivity amounted to 55.6% and specificity was 48.1%. For this cut-off value, the OR was 0.86, and the 95% confidence range extended from 0.29 to 2.54.

Comparison of κ and λ sFLC Concentration in Patients Suffering from MM with and Without Amyloidosis and in the Controls

Abnormal concentrations of κ sFLCs were found in 16 patients with amyloidosis (88.8%); and abnormal λ sFLCs concentrations were found in 14 of them (77.8%). In the group of 52 patients without amyloidosis, abnormal concentrations of κ and λ sFLCs were detected in 44 patients (84.6%) and 24 patients (46.1%) respectively (p = 0.03) (Fig. 8).

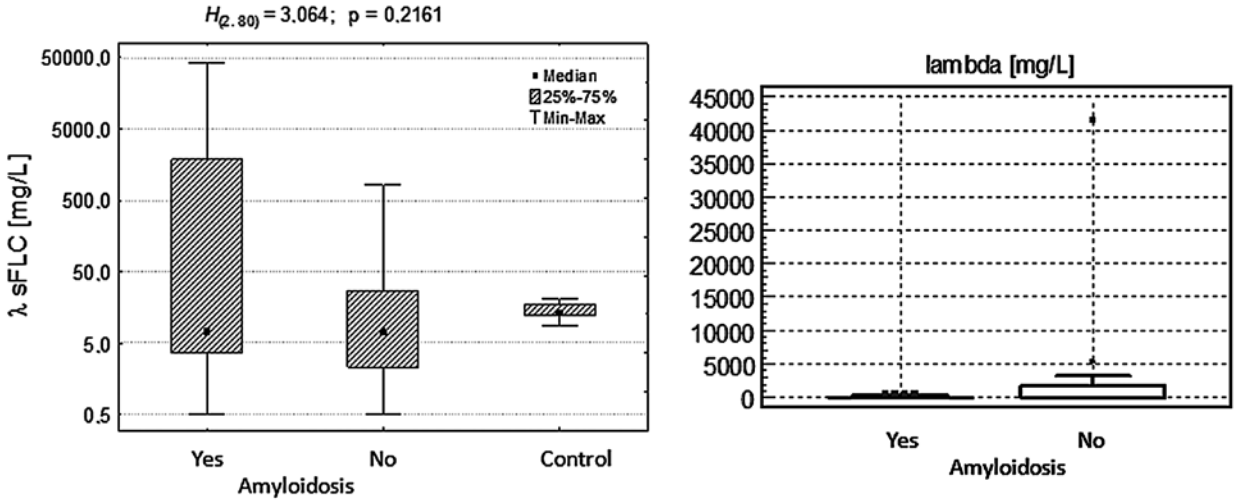

Fig. 6. Concentration of λ sFLCs in MM patients with and without amyloidosis

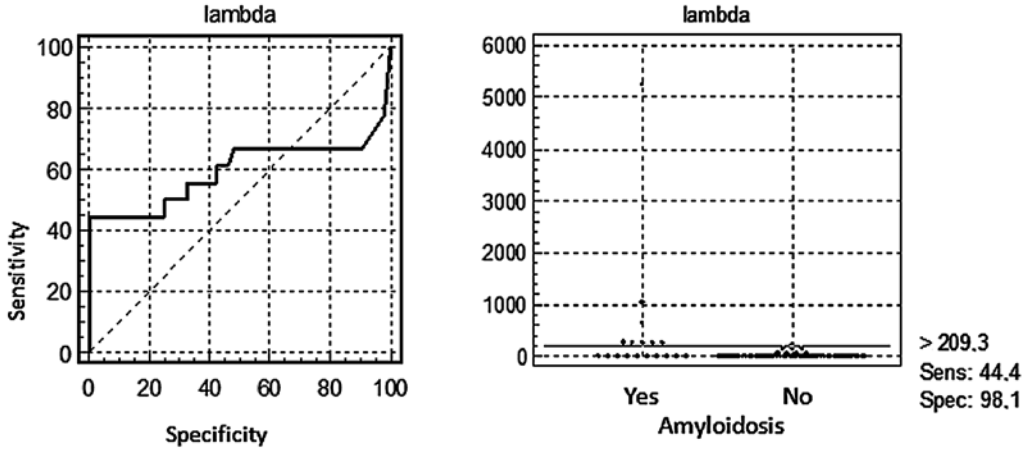

Fig. 7. ROC curve for λ light chains in 70 MM patients

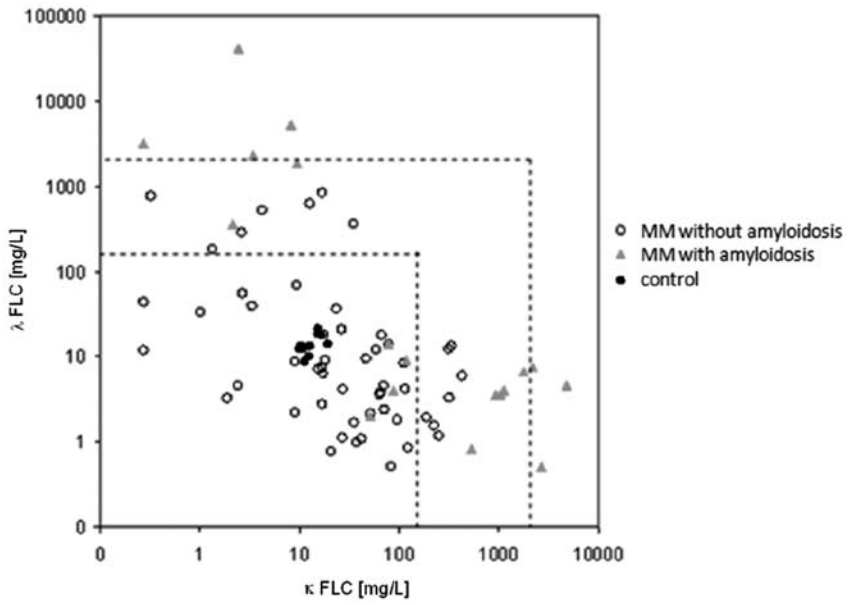

Fig. 8. Concentration of kappa and lambda sFLCs in amyloidosis complicated MM patients, in MM patients without amyloidosis, and in controls

Analysis of the κ/λ Ratio in MM Patients

The value of the κ/λ ratio in MM patients varied from 0.00 to 5235 (x = 139.0, SD = 638.0), and it was significantly higher (p = 0.078) than the ratio in the controls (0.41–1.65, x = 0.97, SD = 0.23). The value of the κ/λ ratio in the 15 renal failure patients varied from 0.00 to 5235 (x = 175.8, SD = = 723.8) and was higher than in MM patients with normal renal function, (0.0 to 158.8, x = 14.8, SD = 40.8, p = 0.078).

Analysis of the κ/λ Ratio in MM Patients with Amyloidosis

The value of the κ/λ ratio in the amyloidosis group ranged from 0.0 to 5235 (x = 465.5, SD = = 1222) and it was significantly higher (p = 0.001) than in the group of MM patients without amyloidosis (0.0–209, x = 26, SD = 46). In both subgroups, the values were significantly higher than in the control group (p = 0.0001). The κ/λ ratio in AL-complicated MM patients, both with and without renal failure, was significantly higher (p = = 0.0014 and p = 0.036 respectively) than in patients without amyloidosis in corresponding subgroups. The value of the κ/λ ratio in all MM patients, both with and without AL, exceeded normal values.

Discussion

Malignant plasma cells produce excessive amounts of one type of light chain, leading to abnormal κ/λ ratio values. In the case of monoclonal kappa proliferation, the ratio value increases, and with lambda proliferation it decreases. In the current study, abnormal concentrations of κ sFLCs were found in 60 out of 70 patients (85.7%). In 45 out of those 60 (75%), the κ sFLCs concentration was above normal limits, and in the remaining 15 (25%) it was below. Abnormal concentrations of λ sFLCs were observed in 38 out of 70 patients (53.2%); in 20 of those 38 (50.5%) it was above normal limits and in 18 (49.5%) it was below. This means that in 65 of the MM patients (91.4%) both κ and λ sFLC concentrations were above the normal limits. The concentration of κ sFLCs was significantly higher in comparison with healthy volunteers (p = 0.0463). However, no statistically significant difference was found between the patients' λ sFLC concentration in comparison with the healthy controls. In 53% of the patients, λ chains values were abnormal; in half of these the values were below normal limits. In 68 out of 70 patients (97.1%), the κ/λ ratio was abnormal. In 49 of them, it was above the values found in the control group and in 19 it was lower. These results are compatible with earlier measurements made in larger groups of patients. Snozek et al. detected abnormal sFLC concentrations in 95% of 576 patients with newly diagnosed myeloma [10], and Dispenzieri et al. found abnormal κ/λ ratios in 96% of patients before treatment onset [11]. The participants in the current study included both newly diagnosed and relapse/progression cases; however, the analysis did not reveal any significant differences between these two subgroups. In a study published by Mead et al., sFLCs levels were 84%, 92% and 94% of IgG, IgA and IgD myelomas respectively [12]. In the present study, no significant differences in sFLCs concentration were observed in relation to the type of myeloma.

In the group of 18 amyloidosis patients, among whom there were 12 and 6 patients with kappa and lambda chains respectively, sFLC concentrations were observed to be significantly higher than in patients without amyloidosis. The first investigation of sFLC concentrations in AL amyloidosis was performed in London in 2003; that study revealed abnormal concentrations of sFLCs in 252 out of 262 patients (98%) [13]. Subsequent analyses by Katzmann et al. and Akar et al. confirmed a high percentage of positive sFLC results in amyloidosis, but abnormal κ/λ ratios were detected in 89% and 73% of the patients respectively, depending on the light chain type [7, 14]. In contrast to the present study, those groups comprised patients whose amyloidosis was not coexistent with myeloma, which accounts for the smaller percentage of patients in whom abnormal κ/λ ratios were detected. According to Cohen et al., 10–15% of AL amyloidosis patients may reveal minimally abnormal or increased sFLC concentrations with a κ/λ ratio within the normal limits [15]. In the present study, concentrations of sFLCs and κ/λ ratio values, in both amyloidosis myeloma and non-amyloidosis myeloma, were dependent on renal function. The highest values of these parameters were observed in patients with both amyloidosis and renal failure. In an animal model, myeloma kidney occurs along with different concentrations of sFLCs, depending on the free chains' physical and chemical qualities, their amino acid constellations or other factors like dehydration or hypercalcemia [16]. In renal failure patients in whom glomerulous filtration has decreased, FLC clearance is lowered, which leads to a prolonging to these chains' half-life and a κ/λ ratio increase [16]. In 74% of amyloidosis patients who do not meet myeloma criteria, nephrotic syndrome develops; however, kidney function may remain normal for some time. If amyloid fiber deposits are present mainly in the vessels, kidney lesions are manifested mainly by proteinuria [16]. In the present study, nephotic syndrome was not diagnosed in any of the patients. Proteinuria and renal failure were observed in five amyloid patients and in 10 patients without this complication. The clinical profile may suggest that in the study group, myeloma-kidney-type lesions developing with renal failure were more predominant than glomerular lesions of the amyloidosis type developing with nephrotic syndrome. A final diagnosis would be possible on the basis of a histopathological assessment of the kidneys, but no such tests were carried out.

A drop in the concentration of serum FLCs correlates with longer survival time, regardless of the chemotherapy applied [16]. In a study by Hutchinson et al., myeloma kidney patients were characterized by a higher sFLC concentration than myelomas with other pathological lesions in the kidneys [17]. A high concentration of serum FLCs is a bad prognostic factor. Dispenzieri et al. published the results of 119 AL amyloidosis patients who underwent megachemotherapy [18]. In the group with higher sFLC concentrations, they observed a significant increase in mortality, as well as a higher number of organ failures. Moreover, a positive correlation between sFLC level and troponin concentration was observed [18]. In 301 analyzed myeloma cases, van Rhee et al. demonstrated that patients in whom sFLCs concentration was higher than 750 mg/L had the worst treatment outcomes. They had significantly higher concentrations of creatinine, beta-2-microglobulin and LDH, as well as higher numbers of plasma cells in the bone marrow [19]. In the present study, in the group of MM patients with amyloidosis, kappa sFLC concentration was found to be correlated positively with LDH and beta-2-microglobulin. Furthermore, the patients with the most advanced lesions due to the progression of amyloidosis had the highest concentration of sFLCs.

Data from Cohen et al. document the significance of free light chains in the development of amyloidosis [20]. They demonstrated that 88% of amyloidosis patients in whom sFLC concentration was reduced by over 50% due to treatment applied survived 5 years. If the reduction in sFLCs was smaller, the five-year survival percentage decreased to 39% of the patients. Additionally, Cohen et al. demonstrated that reductions in sFLC concentration inhibited the formation of new amyloid deposits and existing ones underwent partial regression.

The authors concluded that in myeloma patients the concentration of kappa and lambda free light chains is increased. Amyloidosis is favored by more active myeloma development, which is assessed on the basis of serum LDH and beta-2-microglobulin concentrations. In the data from the current study, the concentration of sFLCs, along with LDH and beta-2-microglobulin concentration, is one of the strong discriminators of amyloidosis development in multiple myeloma patients.

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Conflict of interest: None declared

Received: 11.02.2014
Revised: 14.03.2014
Accepted: 24.06.2014