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The Occurrence of AL Amyloidosis (Light-Chain Amyloidosis) in Patients with Multiple Myeloma in Lower Silesia Region, Poland

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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. The incidence of amyloidosis is difficult to determine because the disease is often undiagnosed or diagnosed incorrectly. In Polish studies, there are no statistics and analyses of the factors that may influence the development of amyloidosis in patients with multiple myeloma
Objectives. The goal of this study was to estimate the incidence of AL amyloidosis in MM patients in Lower Silesia region.
Material and Methods. 70 patients treated at the Department of Hematology, Provincial Hospital in Legnica and the Department of Hematology, Blood Neoplasm and Bone Marrow Transplantation, Medical University in Wroclaw were enrolled in the survey. 37 patients were newly diagnosed, 33 had been treated for 2–34 months. The basis for the diagnosis of amyloidosis was the presence of green colored amyloid deposits in the polarized light microscope in the adipose tissue (received from abdominal fold and stained with Congo red).
Results. Amyloidosis was diagnosed in 18 (25.7%) patients with MM, 9/9 F/M, aged 47–83 years. 6 (33%) pts with amyloidosis had newly diagnosed MM, in 12 (67%) progression of the disease was diagnosed. Amyloidosis occurred significantly more often ($p = 0.048$) in already treated patients. The odds ratio (OR) was 2.95. Amyloidosis occurred most frequently in patients with IgG myeloma (67%), (OR = 1.98), was more often found in patients with kappa light chain versus lambda, respectively 67% and 33%. The probability of amyloidosis in patients with clinical stage III was 1.5 times higher ($p = 0.05$) than in other stages (OR = 1.5), in persons with renal dysfunction was twice as high (OR = 2.4) compared to the renal competence group ($p = 0.05$).
Conclusions. AL amyloidosis in the course of MM occurs in Lower Silesia region with a comparable rate to other regions of the world. It is significantly more often diagnosed in patients with relapsed or refractory disease, in persons with clinical stage III and with renal failure (**Adv Clin Exp Med 2014, 23, 2, 235–244**).

Key words: amyloidosis, multiple myeloma, epidemiology, Lower Silesia, Poland.

Amyloidosis is an inherited or acquired systemic storage disease in which pathologic, amorphous substance produced as a result of abnormal protein metabolism and resistant to proteolysis is deposited in the extracellular space of various tissues (intracellular deposits occur rarely). This leads to the destruction of normal tissue structure and disturbs its function. The disease may affect one or several organs simultaneously and is always fatal [1-3].

Depending on the number of plasma cells in the bone marrow, the level of monoclonal protein in the serum and/or urine or the presence of osteolytic changes, we can diagnose either AL, or AL

in the course of myeloma (and other monoclonal gammapathies). Kyle demonstrated that 85% of patients diagnosed with AL amyloidosis meet the criteria of various forms of plasma cell dyscrasias, while the remaining 15% lack clinical symptoms of plasma cells clonal growth. [2] According to Abraham, all patients with AL amyloidosis reveal monoclonal gammapathy on the basis of serum free light chains evaluation. [4] AL amyloidosis affects organs originating from the mesoderm tissue (the heart, digestive tract, peripheral nervous system, skin, tongue).

The incidence of amyloidosis is difficult to determine because the disease is often undiagnosed or diagnosed incorrectly. In order to determine AL amyloidosis prevalence, Kele et al. analyzed the occurrence of the disease in one district in Minnesota in the period from 1952 to 1992. They found the annual incidence of amyloidosis in 8.9 per million in the region. [5] This was the basis for the estimates, according to which, every year, in the United States, 1275–3200 new cases of AL amyloidosis are recognized, which is 5.1–12.8 cases per million people. Studies have shown that in the U.S. and Western Europe, systemic AL amyloidosis is more common. [6] The incidence of this disease is estimated at 0.8–1/100 000 persons / year, patients aged 50–70 years. [7]

There is no center in Europe that would record cases of amyloidosis. The data published in each country determines the incidence of amyloidosis in the particular region. [8] The incidence of AL amyloidosis in the UK is 600 per year. Occasionally, there is a concomitant amyloidosis with IgM paraproteinemia. According to the report of the UK National Amyloidosis Centre, in the period from 1988 to 2006, this kind of incidence was observed in 103 patients.

Studies have shown that in 10–20% of patients with multiple myeloma contributes to the development of AL amyloidosis. [9,10] Primary AL amyloidosis also occurs in 7% of patients with nonhematologic cancers. [11]

Amyloidosis is a rare disease which affects patients before the age of 40 and is more common in men (50–65%). Those aged 50–70 years accounted for 60% of patients. [7] The primary amyloidosis confirmatory diagnostic test is a biopsy of adipose tissue from the abdominal fold and a demonstration in the downloaded material (after staining with Congo red light) a characteristic birefractive polarized light, or unbranched fibrous structures with a diameter of 10 nm by an electron microscopy. If the test result is negative, the biopsies of salivary gland, rectal mucosa, gums or bone are suggested. Percentage identification of amyloid in other locations is varied: biopsies of kidney, spleen or liver are positive in more than 90%, of the aspirations of abdominal fat in 60–80%, rectal biopsy in 50–70%, bone marrow biopsy in 50–55%, whereas skin biopsy is positive in 50–80%. [12] To visualize the amyloid deposits, radioisotope methods are used e.g. technetium Tc 99m which proves particularly useful in cardiac amyloidosis identification. It is applied in a very advanced stage of cardiomyopathy and, along with echocardiography, provides a diagnosis basis. Scintigraphy is another diagnostic method of amyloid deposits. It takes advantage of the co-existence of amyloid deposits with normal serum protein SAP, which can be labeled with technetium or iodine (I^{123}).

The most common clinical manifestations of amyloidosis include loss of body weight, ankle swelling, hoarseness, paresthesia, fatigue, orthostatic blood pressure drops, heart failure, enlarged liver or tongue and carpal tunnel syndrome [13]. In the course of AL amyloidosis, kidneys and the heart are mostly affected, and the development of peripheral neuropathy as well as damage of the central nervous system are observed. [6] According to Meller, kidney damage in the form of nephrotic syndrome occurs in 28% of patients, heart failure and peripheral neuropathy in 17%, carpal tunnel syndrome in 21%, orthostatic hypotension in 11%, and orbital purpura in 15% of patients [14].

The goal of this study was to estimate the incidence of AL amyloidosis in patients with multiple myeloma in the province of Lower Silesia, Poland.

Material and Methods

The study was approved by the Ethics Committee of the Medical University of Wroclaw. Each patient received detailed information about the purpose of the tests and signed a consent form. 70 patients with multiple myeloma treated at the Department of Hematology, Provincial Hospital in Legnica and the Department of Hematology, Blood Neoplasms and Bone Marrow Transplantation, Medical University in Wroclaw were enrolled in the survey. Among them, 37 pts were newly diagnosed and had not been treated and 33 persons had been treated for 2–34 months with VAD, CVMBP, CTD or MP.

The diagnosis of multiple myeloma was determined on the basis of bone marrow cytology, and/ /or histopathology of trephine biopsy or solitary tumor, the presence of proteins or monoclonal light chains in serum and/or urine and osteolytic lesions shown on X-rays or by magnetic resonance imaging. The basis for the diagnosis of amyloidosis was the presence of green colored amyloid deposits in the polarized light microscope in the adipose

tissue (received from abdominal fold and stained with Congo red).

Basic descriptive statistics were used to describe all quantitative variables. The arithmetic mean, standard deviation, minimum and maximum values were used. A comparison of data among the groups was performed using the exact Fischer test, the chi-square test, as well as the t-student test. The Kaplan-Meyer curve was used for estimating the overall survival (OS). In order to estimate the thresholds of quantitative variables for patient differentiation, Receiver Operating Characteristic (ROC) analysis was performed. The odds ratio (OR) was calculated for each threshold. In all analyses carried out, *P* value 0.05 was considered statistically significant. Statistical evaluation was performed using Microsoft Office EXCEL and Statistica software.

The characteristics of the study group are present in Table 1.

Table 1. Clinical and laboratory data of the patients

Number	70
Age (years, median, range)	x = 61.1, SD = 11.1, range: 28–83
Sex F/M	40/30
Newly diagnosed MM/Disease progression/refract	37/33
Multiple Myeloma: IgG/IgA/IgM/LCD	34/16/4/6
Non-secretory MM	6
Other (solitary MM)	4
Light chain type K/L	45/19
Stage of the disease IA/IIA/IIB/IIIA/IIIB/non-defined	1/22/3/27/12/5
Kidney function A/B	55/15
OS median	40

* LCD – light chain disease.

Material

The adipose tissue samples were harvested by needle aspiration of the abdominal area, and 10 mL of blood were collected to clot to obtain serum.

The analysis used the results of routine testing in all patients to determine the disease stage and was performed according to the standards of the hospital laboratory. Historical data of co-existent diseases were used and, in the case of refractory or relapse, multiple myeloma patients, information about prior causative treatment was exploited.

Test of Amyloid in the Adipose Tissue

Aspirate material was mottled on a slide and after 1 h of drying, it was Congo red stained and then evaluated in a polarized light microscope.

Results

The Occurrence of Amyloidosis in the Study Group

Amyloidosis was diagnosed in 18 (25.7%) patients with multiple myeloma, nine women and nine men, aged 47–83 years, Me = 66, x = 63.5 years, SD = 9.4.

Example of green glowing amyloid plaque in polarizing microscope light is presented in Fig. 1.

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

Six (33%) patients with amyloidosis had newly diagnosed MM, in the remaining 12 (67%) progression or relapse of the disease was diagnosed. In the study group, amyloidosis occurred significantly more often (p = 0.048) in already treated patients with the disease refract or progression. In the patients with refractory MM the odds ratio (OR) was 2.95 (95% confidence interval: from 1.03 to 9.21.) This means that the probability of amyloidosis in patients with relapsed and refractory disease was 3 times greater than in the case of newly diagnosed ones (Table 2).

In 52 (74.3%) patients with myeloma, including 31 women aged 28–81 years, Me – 62 years, x = 61.8 years, SD = 11.7, there was no presence of amyloid. There was no evidence of amyloidosis in any of 4 patients with solitary myeloma. Due to the small number of patients they were included in

Table 2. Relationship between duration of the disease and risk of amyloidosis

	Group I (with amyloidosis) n = 18	**Group II (without amyloidosis) n = 52**	**Result**
Number (%) of patients:			
RRMM	12 (67%)	21 (40%)	$p = 0.049$
Newly diagnosed	6 (33%)	31 (60%)	
OR = 2.95 (1.03 do 9.21)			

the group of multiple myeloma without amyloidosis. Among MM patients without amyloidosis, there were 31 (60%) persons with newly diagnosed and 21 (40%) with refractory/relapsed MM (RRMM).

Comparison of Selected Clinical Parameters in Patients with Multiple Myeloma with Amyloidosis and Without this Complication

In the study group, amyloidosis occurred most frequently in IgG MM pts (67%). The probability of amyloidosis in patients with this type of myeloma was two times higher than in other patients (OR = 1.98) (Table 3). Quite similarly, amyloidosis was more often found in patients with kappa light chain versus lambda, respectively 67% and 33%. The probability of amyloidosis in patients with clinical stage III was one and a half times higher (p = 0.05) than in other stages (OR = 1.5). The percentage of patients with renal failure in amyloid and no amyloidosis groups was respectively 28% and 19% The probability of amyloidosis presence in patients with renal dysfunction was twice as high (OR = 2.4) compared to the renal competence group (p = 0.05). In patients with multiple myeloma complicated by renal failure and amyloidosis, renal amyloidosis should be considered as a cause of renal failure. During the study, however, no renal biopsy was performed revealing glomerular lesions.

There was no statistically significant correlation between amyloidosis prevalence and patients' age and sex.

Analysis of Amyloidosis Symptoms in the Study Group

Abnormalities characteristic for amyloidosis were considered. The incidence of symptoms in patients with MM complicated by amyloidosis and without this complication was compared. No significant differences were analyzed in the manifestation of symptoms. Some of the symptoms, such as periorbital ecchymosis or large tongue spectacles, were present only in the group with amyloidosis (Table 4).

Occurrence of Amyloidosis in Patients with Refractory/ /Relapsed Myeloma Depending on the Duration and the Type of Cytostatic Therapy

A separate analysis was made for a group of 33 patients with refractory and/or relapsed multiple myeloma, including 12 patients with amyloidosis and 21 without this complication. The duration of cytostatic treatment, the number of lines as well as the type of treatment carried out was taken into account. It revealed the tendency (p = 0.06) of a higher incidence of amyloidosis (OR 2.81, 3.03) in patients who received more than two lines of VAD treatment. Treatment with CVMBP, CTD or MP was not associated with a higher risk of amyloidosis (OR respectively 1.57, 0.37 and 1.04.) Thorough analysis of amyloidosis prevalence in respect to the cytostatic therapy is presented in Table 5.

Occurrence of Amyloidosis in Patients with Multiple Myeloma Depending on Comorbidity and Treatment

In the whole group of patients with multiple myeloma, comorbidities were found including heart disease and cardiovascular disease, diabetes or chronic inflammatory conditions. An analysis was carried out to determine these diseases and their treatment impact on the formation of AL amyloidosis. There was no significantly higher incidence of amyloidosis in myeloma patients with ischaemic heart disease with or without myocardial infarction, hypertension, diabetes or chronic inflammatory. Adjusted odds ratio ranged from 0.45 to 1.84 for the selected comorbidities.

Quite similarly, analysis of the effect of selected

Table 3. Relationship between type of myeloma, type of light chain as well as renal function and risk of amyloidosis

	Group I (with amyloidosis)	**Group II (without amyloidosis)**	**Result**
Number n:	18 (100%)	52 (100%)	
MM type:			
IgG	12 (66.6%)	22 (42.3%)	$p = 0.2278$ OR = 1.98 (0.66 do 5.92)
other	6 (33.4%)	30 (57.7%)	
kappa (κ)	12 (67%)	33 (63%)	$\chi^2_{v=2} = 2.44$ $p = 0.295$
lambda (λ)	6 (33%)	13 (25%)	
Non secretory	0 (0%)	6 (12%)	
Disease stage:			
stage IA	0 (0%)	1 (2%)	$\chi^2_{5=v} = 16.2$ $p = 0.761$
stage IIA	8 (44%)	14 (26%)	
stage IIB	0 (0%)	3 (6%)	
stage IIIA	5 (28%)	22 (42%)	
stage IIIB	5 (28%)	7 (14%)	
undefined	0 (0%)	5 (10%)	
Comparison of stages			
in stage III	10 (56%)	29 (56%)	$p = 0.5928$ OR = 1.51 (0.53 do 4.46)
in stage I or II	8 (44%)	23 (44%)	
with renal failure	5 (28%)	10 (19%)	$p = 0.05$ OR = 2.39 (0.71 do 8.05)
without renal failure	13 (72%)	42 (81%)	

Table 4. The incidence of some symptoms in MM patients with diagnosed amyloidosis (Group I) and without this complication (Group II)

Number of patients (%)				**Test result**
Symptoms	**Group I n = 18**	**Group II n = 52**	**Total n = 70**	**P**
Oedema	4 (22%)	6 (12%)	10 (14%)	0.468
Orthostatic hypotension	4 (8%)	1 (6%)	5 (7%)	0.820
ECG findings	5 (28%)	24 (46%)	29 (41%)	0.277
Enlargement of the heart (ECG, ultrasound)	2 (11%)	5 (10%)	7 (10%)	0.512
Hepatomegaly	1 (6%)	3 (6%)	4 (6%)	0.579
Spleen enlargement	0 (0%)	2 (4%)	2 (3%)	0.981
Diarrhea	0 (0%)	5 (10%)	5 (7%)	0.404
Skin changes	1 (6%)	2 (4%)	3 (4%)	0.714
Chronic inflammation	2 (11%)	6 (12%)	8 (11%)	0.703
Tongue enlargement	1 (6%)	0 (0%)	1 (1%)	0.578
Polyneuropathy	4 (22%)	4 (8%)	8 (11%)	0.215
Hemorrhages	1 (6%)	3 (6%)	4 (6%)	0.579
Proteinuria	4 (22%)	7 (13%)	11 (16%)	0.614
Paresthesia	0 (0%)	5 (10%)	5 (7%)	0.404
Cachexia	5 (28%)	8 (15%)	13 (19%)	0.376
Periorbital ecchymoses	1 (6%)	0 (0%)	1 (1%)	0.578
Impotence	2 (4%)	0 (0%)	2 (3%)	0.960

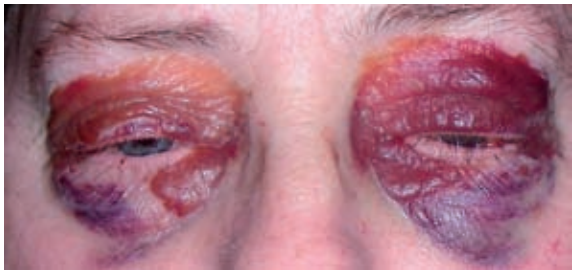

Fig. 2. Periorbital ecchymoses in a patient with IgG MM and AL amyloidosis

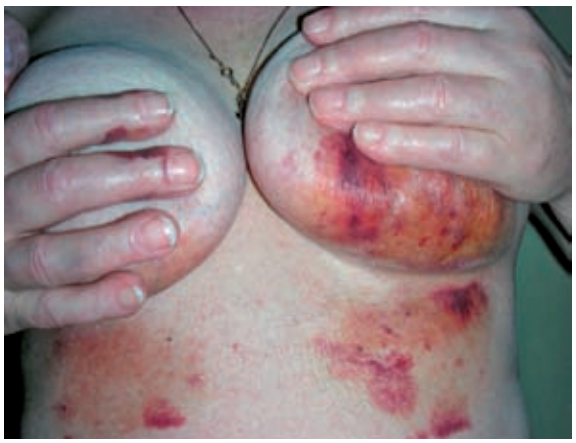

Fig. 3. Ecchymosis in a patient with IgG myeloma complicated by AL amyloidosis

drugs used in the treatment of chronic comorbidities was made. There were no significant differences in the incidence of amyloidosis in myeloma patients using such treatment as insulin, oral hypoglycemic agents, ACE inhibitors, diuretics and inotropic agents – odds ratios ranged from 0.38 to 3.0 for the different classes of drugs. Detailed data is presented in Table 6 and 7.

Comparison of BMI in Patients with Multiple Myeloma Based on the Occurrence of Amyloidosis

In the group of amyloidosis myelomas, BMI ranged from 20.8 to 27.4 (x = 23.6, SD = 2.3) and was not significantly different from the values reported in patients without amyloidosis: from 17.2 to 29.6, (x = 23.7, SD = 2.6).

Amyloidosis Influence on Survival Time in Patients with Multiple Myeloma

There was no statistically significant difference in overall survival time between multiple myeloma patients with amyloidosis and without one (p = 0.49) (Fig. 4).

Discussion

Congo red staining of adipose tissue taken from the abdominal fold and the characteristic bi-

Table 5. Relationship between cytostatic therapy and the risk of mayloidosis

Therapy line	MM Patients with amyloidosis n = 12	MM Patients without amyloidosis n = 21	OR (95% confidence interval)	Chi-square test or Fisher's exact test
Treatment > 12 months	14 (77.8%)	37 (71.2%)	1.42 (0.40 ÷ 5.02)	Fisher's exact test: $p = 0.4154$
Treatment ≤ 12 months	4 (22.2%)	15 (28.8%)	1 (ref.)	
Number of lines > 2	13 (72.2%)	25 (48.1%)	2.81 (0.87 ÷ 9.01)	Fisher's exact test: $p = 0.0658$
Number of lines ≤ 2	5 (27.8%)	27 (51.9%)	1 (ref.)	
Treated with VAD	13 (72.2%)	24 (46.2%)	3.03 (0.94 ÷ 9.74)	Fisher's exact test: $p = 0.0658$
Not treated with VAD	5 (27.8%)	28 (53.8%)	1 (ref.)	
Treated with CVMBP	7 (38.9%)	15 (28.8%)	1.57 (0.51 ÷ 4.82)	$\chi^2 = 0.247$
Not treated with CVMBP	11 (61.1%)	37 (71.2%)	1 (ref.)	$p = 0.619$
Treated with CTD	9 (50.0%)	38 (73.1%)	0.37 (0.12 ÷ 1.12)	$\chi^2 = 2.266$
Not treated with CTD	9 (50.0%)	14 (26.9%)	1 (ref.)	$p = 0.132$
Treated with MP	5 (27.8%)	14 (26.9%)	1.04 (0.31 ÷ 3.47)	Fisher's exact test: $p = 1.000$
Not treated with MP	13 (72.2%)	38 (73.1%)	1 (ref.)	

Table 6. The occurrence of amyloidosis in patients with multiple myeloma based on comorbidities

Number (%) of patients:	**Group I (with amyloidosis) n = 18**	**Group II (without amyloidosis) n = 52**	**Test result**
With coronary artery disease	5 (28%)	10 (19%)	$\chi^2_{v=1} = 0.18$ $p = 0.668$
Without coronary artery disease	13 (72%)	42 (81%)	
OR = 0.09 (0.03 do 0.32)			
With myocardial infarction	3 (17%)	4 (8%)	$\chi^2_{v=1} = 0.41$ $p = 0.523$
Without myocardial infarction	15 (83%)	48 (92%)	
OR = 2.40 (0.48 do 11.95)			
With heart failure	2 (11%)	4 (8%)	$\chi^2_{v=1} = 0.002$ $p = 0.967$
Without heart failure	16 (89%)	48 (92%)	
OR = 1.50 (0.25 do 8.98)			
With artery hypertension	9 (50%)	23 (44%)	$\chi^2_{v=1} = 0.02$ $p = 0.882$
Without artery hypertension	9 (50%)	29 (56%)	
OR = 0.79 (0.27 do 2.32)			
With ECG changes	5 (28%)	24 (46%)	$\chi^2_{v=1} = 1.18$ $p = 0.277$
Without ECG changes	13 (72%)	28 (54%)	
OR = 0.45 (0.14 do 1.44)			
With diabetes	5 (28%)	9 (17%)	$\chi^2_{v=1} = 0.38$ $p = 0.538$
Without diabetes	13 (72%)	43 (83%)	
OR = 1.84 (0.52 do 6.46)			
With chronic inflammation	2 (11%)	6 (12%)	$\chi^2_{v=1} = 0.15$ $p = 0.704$
Without chronic inflammation	16 (89%)	46 (88%)	
OR = 0.96 (0.18 do 5.24)			

Table 7. Occurrence of amyloidosis in myeloma patients depending on the treatment of concomitant diseases

Number (%) of patients:	**Group I n = 18**	**Group II n = 52**	**Test result**
With ACE inhibitors	3 (22%)	13 (12%)	$\chi^2_{v=1} = 0.16$ $p = 0.689$
Without ACE inhibitors	15 (78%)	39 (88%)	
OR = 0.60 (0.15 do 2.41)			
With diuretics	5 (28%)	25 (48%)	$\chi^2_{v=1} = 1.50$ $p = 0.221$
Without diuretics	13 (72%)	27 (52%)	
OR = 0.42 (0.13 do 1.33)			
With inotropes	3 (17%)	18 (35%)	$\chi^2_{v=1} = 1.29$ $p = 0.257$
Without inotropes	15 (83%)	34 (65%)	
OR = 0.38 (0.10 do 1.48)			
With insulin	1 (17%)	1 (35%)	$\chi^2_{v=1} = 0.001$ $p = 0.981$
Without insulin	17 (83%)	51 (65%)	
OR = 3.00 (0.18 do 50.6)			
With Diaprel	2 (22%)	7 (12%)	$\chi^2_{v=1} = 0.02$ $p = 0.879$
Without Diaprel	16 (78%)	45 (88%)	
OR = 0.80 (0.15 do 4.28)			

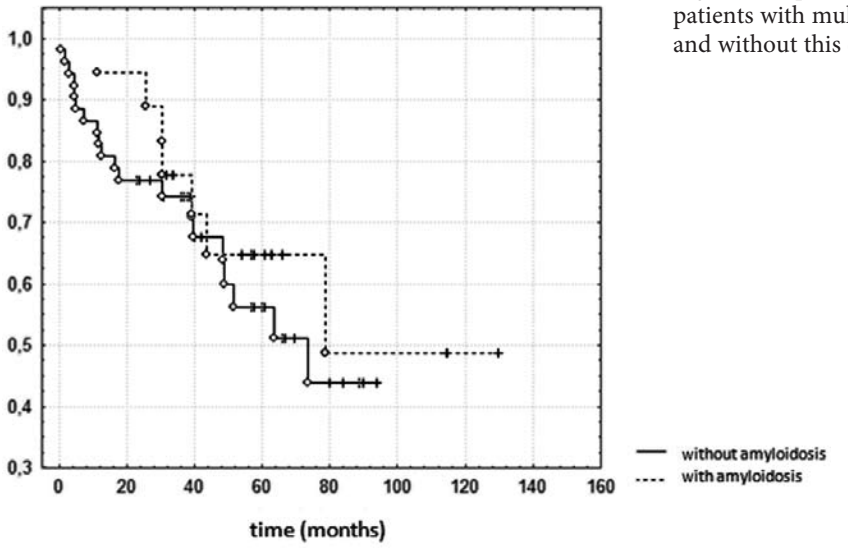

Fig. 4. Comparison of the Kaplan-Meier curves of patients with multiple myeloma with amyloidosis and without this complication

refractive polarized light shining is, for more than 40 years, the gold standard in the diagnosis of amyloidosis and is the most preferred method to show the presence of amyloid deposits. [15]

Despite the simple and good diagnostic tool, amyloidosis is not recognized in all patients, and its occurrence is considered to be undervalued. There are no statistics and analyses of the factors that may influence the development of amyloidosis in patients with multiple myeloma in Polish studies. In the mid-nineties, in research carried out on the U.S. population, Rajkumar estimated the occurrence of AL amyloidosis in 5–10% of cases with newly diagnosed plasma cell dyscrasias. [16] Vela – Ojeda in 2009 in the Mexican material found amyloidosis in 68/201 (34%) of newly diagnosed myelomas. [17] On the other hand, a retrospective analysis conducted at the Mayo Clinic found that 40% of patients with AL amyloidosis had more than 10% plasma cells in bone marrow. [18]

Studies carried out on patients with plasma cells dyscrasias in Lower Silesia region revealed the presence of amyloidosis in 18/70 (25.7%) patients and similarly to the studies of the American group, in 8.6% of people with newly diagnosed disease. Amyloidosis was found significantly more often in patients with relapsed or refractory disease treated, especially with VAD, for more than 12 months. In our material, amyloidosis occurred most frequently in patients with IgG kappa myeloma, but patients with this type of myeloma were most strongly represented group. In the study conducted by Desikan, including 81 patients with multiple myeloma, amyloidosis was found in 32 (38%) patients, and just like in our group, there was no dominance of lambda chain. [19] The study made by Madan involving 47 patients with myeloma complicated by amyloidosis, ratio of kappa to lambda was 1:2 and was closer to that of AL amyloidosis running without symptomatic myeloma [20]. In amyloidosis without evidence of proliferation of plasma cells, lambda chain is more common (1:3), which according to some authors, suggests the existence of embryonic Vλ gene associated with amyloid. In this study, amyloidosis was found in 9/40 women and 9/30 men and, as in other studies, a slight superiority in number of men with this complication was found. [17] In the study by Madan, AL amyloidosis was diagnosed in 47/4318 patients with multiple myeloma, including 29 (62%) of men. [20] Amyloidosis, such as multiple myeloma, is rare in patients under 40 years of age. Among 800 patients with amyloidosis, both women and men, seen in the National Health Service and the National Amyloidosis Centre in the UK, 66% were at the age of 50–70, 17% were younger than 50 years and only 3% were under the age of 30. Our study also showed no difference in age between the group with amyloidosis and without this complication, patients with amyloidosis were at the average age of 63.2. Clinical manifestations of amyloidosis occurred in 12 patients, including seven with acute illness and five patients with relapsed one. In 7 patients, an enlarged heart and/or changes in the ECG were found, and these were the most common complications. Proteinuria, oedema, and peripheral neuropathy occurred in 4 patients. Thus, the heart, kidneys and nervous systems were, like in AL amyloidosis without myeloma, most commonly affected organs in the course of the disease.

In patients with enlarged heart, or changes in ECG, other reasons for the deviations were excluded and it was assumed that they could be secondary to amyloidosis, although not confirmed by bioptic examination and troponin level control. The

occurrence of cardiac amyloidosis is one of the most unfavorable prognostic factors, with an estimated overall survival time of 1.1 years after the diagnosis of amyloidosis and 0.75 years after the onset of heart failure [21]. In one patient, a large tongue, hematomas and periorbital ecchymoses characteristic for amyloidosis were observed. Noteworthy is the fact that 6/18 (33%) patients showed no clinical signs of amyloidosis, while a body fat test proved positive, and the presence of amyloidosis was confirmed by the study of free light chains in serum.

In our study, amyloidosis was significantly more common in patients with refractory/relapsed multiple myeloma. The treatment course was analyzed in 12 patients with amyloidosis and compared to 21 patients free of this complication. There were no significant differences in the treatment in both compared groups. There was only a trend ($p = 0.06$), which showed that patients treated with more than two lines, and treated with VAD, presented amyloidosis more frequently. In the available literature, there are no similar studies. These results deserve further attention especially due to the fact that the study group is small.

Chronic inflammation, chronic infection and diseases associated with activation of B lymphocytes, with polyclonal hypergammaglobulinaemia and increased concentration of polyclonal FLCs may contribute to the development of amyloidosis, especially AA one.

The distinction between AL amyloidosis AA in certain clinical conditions may be difficult. Some examples of diagnosis of AL amyloidosis in patients with suspected AA amyloidosis were presented [22]. Additionally, certain chronic inflammatory diseases proceed with the presence a monoclonal protein and are complicated by AA or AL amyloidosis [23]. This led some investigators to recommend testing both in the light chain and AA amyloidosis, especially in renal amyloidosis [24]. Our tested material was analyzed in terms of the coexistence of other chronic diseases that could contribute to the development of AL amyloidosis in patients with multiple myeloma. None of the patients had autoimmune disease. Patients with amyloidosis were burdened with comorbidities no more than those with myelomas without amyloidosis.

Also, medications, most often ACE inhibitors, diuretics and inotropic drugs were inconsequential in the development of amyloidosis. Moreover, they were recommended in the treatment of cardiovascular disease in the course of cardiac amyloidosis.

Demonstration of amyloidosis in patients with multiple myeloma is an unfavorable prognostic factor, regardless of the presence or absence of symptoms at the time of amyloidosis diagnosis [17]. Abraham showed that the median survival time of patients with multiple myeloma complicated by amyloidosis was 1.1 years compared to 2.9 years without amyloidosis. [25]

In our study, however, in a 39 month follow-up, the survival time of patients with multiple myeloma both complicated by amyloidosis and without amyloidosis did not differ significantly. Also in the analysis presented by Madan, in 2010, survival times in patients with myeloma complicated with amyloidosis were not different from those in patients without one [20]. Also, the studies by Desikan, Vela Ojeda and Bahlis are noteworthy. The authors demonstrated that the prevalence of amyloidosis does not affect the results of assisted megachemotherapy followed by single or tandem autologous transplantation in myeloma patients [17, 19, 26]. The authors emphasize, however, that cardiac amyloidosis and multi-organ changes may be associated with high peritransplantation mortality. Among our patients, none of them underwent megachemotherapy and autologous stem cell transplant.

In conclusion, it should be noted that AL amyloidosis in the course of multiple myeloma occurs in Lower Silesia with a comparable rate as in other regions of the world, where similar analyses were performed. Cytostatic therapy conducted over two lines, progression of the disease, can promote the formation of amyloid. Diabetes melitus, chronic heart disease and drugs used in the treatment of these conditions do not affect the formation of amyloid fibres in patients with plasma cell dyscrasias. However, these observations require confirmation in a larger group of patients.

It is noteworthy that in some patients with plasma cell dyscrasias, despite the development of amyloidosis, no clinical signs of amyloidosis were demonstrated, that is why testing for the presence of fat amyloid in all patients with newly diagnosed multiple myeloma and in relapsed disease should be considered.

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