

Epidemiological and biological parameters of monoclonal plasma cell dyscrasias in thirty one patients consulting a Moroccan Pasteur Institute.

Abstract

Aims: The current retrospective study aimed to describe epidemiological and biological features of thirty one patients with monoclonal plasma cell dyscrasias. Our study aimed also to compare our results with those from similar institutions in Morocco and other countries and to evaluate the degree of awareness of patients of the importance to follow up their diseases. The patients consulted the Moroccan Pasteur Institute in Casablanca during a period of two years and four months.

Place and duration of study: Laboratory of immunochemistry, Pasteur institute, Casablanca, Morocco. From April 2006 to July 2006.

Methodology: Thirty one files of patients were gathered having a monoclonal peak of gamma or beta globulin demonstrated by urine or serum protein electrophoresis, and subjected on immuno-electrophoresis for detection the type of immunoglobulin responsible for the investigated disorder.

Results: The mean age of the patients was 54.7 ± 10.7 years (range, 26–72 years) and predominance of female individuals was remarked with a sex ratio 0.82. The prevalence of plasma cell dyscrasias increased with the age for both sexes. 66.67% of the patients had a monoclonal gamma globulin peak revealed by electrophoresis. According the results of performed agar gel immuno-electrophoresis, 48% of them had monoclonal immunoglobulin G (IgG) antibodies, followed by class IgA with 29% of cases. Moreover, 55 % of the patients were Kappa-chain positive, while 45% were Lambda-chain positive. Our study showed that the majority of patients didn't follow up the progression of their monoclonal gammopathies by biological tests. However, the assessment of prognostic factors of some patients demonstrated an acceleration of erythrocyte serum rate (66.66% of cases), anemia (50% of cases), an increase of calcium serum levels (37.5% of cases) and $\beta 2$ -microglobulin serum levels were higher than 2.4 mg/l (33.33% of cases). In addition, the median concentration of proteins was 91 g/l (58.62 % of cases), low levels of albumin below 36 g/l were observed (62.96% of cases) and the monoclonal component level was above 30 g/l (55.56 % of cases).

Conclusion: Some of our records were different from those of other series: our patients were younger with a slight predominance of female individuals. Others were consistent namely the monoclonal gamma globulin peak was more frequently observed, and the most common isotype of plasma cell disorders was Ig G. Our study showed also the interest of electrophoresis and immuno-electrophoresis to detect monoclonal gammopathies. However, it was revealed that the two techniques weren't sufficient for diagnosis. On the other hand, an increase in prognostic factors levels was also noted except for the biological test C-reactive protein. Nevertheless, our study pointed out

that the majority of patients didn't have a rigorous monitoring of their disorders by carrying out hematological and serological examinations.

Keywords: *Plasma cell dyscrasias, electrophoresis, immuno-electrophoresis, prognostic factors.*

Abbreviations: **PCD:** *plasma cell dyscrasias*, **MG:** monoclonal gammopathy, **MM:** multiple myeloma, **WM:** Waldenström macroglobulinemia, **MGUS:** monoclonal gammopathy of undetermined significance, **CLL:** chronic lymphocytic leukemia **CRP:** C-reactive protein, **Ig:** immunoglobulin, **β2-m:** beta-2-microglobulin.

1. Introduction

Plasma cell dyscrasias (PCDs) are a variety of disorders characterized by monoclonal proliferation and accumulation of lymphoplasmacytic cells in the bone marrow and, sometimes, tissue deposition of monoclonal immunoglobulins or their components [1]. These monoclonal gammopathies (MG) include a wide range of hematological conditions ranging from benign disorders such as monoclonal gammopathy of undetermined significance (MGUS) to malignant diseases. For instance, multiple myeloma (MM), smoldering multiple myeloma (SMM), Waldenström macroglobulinemia (WM), amyloid light-chain (AL) amyloidosis, POEMS syndrome, non- Hodgkin lymphoma (NHL) and B-cell chronic lymphocytic leukemia (B-CLL) [1, 2, 3]. These diseases may be difficult to diagnose because they affect many tissues and exhibit generally non-specific symptoms [4]. Thus, the basis of the diagnosis is the detection of an abnormal monoclonal paraprotein in the serum and/or urine, by means of electrophoresis and immuno-electrophoresis [2]. Since then, the definitive diagnoses of PCDs require a multidisciplinary approach including bone marrow biopsy, clinical assessment, radiology and clinical laboratory assays [4]. Furthermore, plasma cell labeling index, karyotypic abnormalities molecular alterations, analysis of beta-2-microglobulin and C-reactive protein levels are laboratory prognostic parameters, related to the intrinsic malignancy of the plasma cells, which indicate the risk of transformation from benign to malignant forms, and therefore designate the follow-up and treatment of each individual patient [5].

In the current retrospective study, we reviewed the epidemiological and biological features of patients with plasma cell dyscrasias, established during the period between January 2004 and April 2006 in the Moroccan Pasteur Institute (Casablanca), and we compared our results with those from similar institutions in Morocco and other countries.

2. Materials and methods

2.1. Study location and patients

The current retrospective study was conducted in Pasteur Institute, Casablanca, Morocco, by reviewing records of patients consulting immunochemistry laboratory during the period from 1 January 2004 to 30 April 2006.

This laboratory received requests for urine or serum protein electrophoresis and immuno-electrophoresis for various diseases: myeloma, immune deficiencies, hepatic insufficiency, systemic diseases and rheumatology...

Only patients who had a gamma or beta (rarely alpha 2) monoclonal peak and a monoclonal immunoglobulin demonstrated by urine or serum protein electrophoresis and immuno-electrophoresis, respectively, were retained. The choice of these two techniques was based on the necessity for detection of monoclonal gammopathies affection.

During the period of study, 1758 electrophoreses and 99 immuno-electrophoreses were gathered.

Any double immuno-electrophoresis or non-coupled to electrophoresis was excluded. Thus, our population was limited to 31 patients. Their distribution was done by taking into consideration the age, sex, nature of spike and the type of immunoglobulin heavy and light chains.

Moreover, to detect whether patients had followed up the evolution of their diseases, some prognostic factors were also evaluated such as erythrocyte sedimentation rate, C-reactive protein (CRP), serum levels of calcium, β 2-microglobulin, hemoglobin and some other proteins.

It should be noted that bone marrow biopsies were performed in the clinic that sent the patients sera for testing in the laboratory. We didn't get the results of these analyses.

Statistical analysis was performed by calculation of percentages and arithmetic mean.

3. Results

Our current investigation was a retrospective study that included 31 Moroccan patients having the risk to develop plasma cell dyscrasias consulting Pasteur Institute, Casablanca, between January 2004 and April 2006.

Detailed epidemiological and clinical characteristics of 31 patients are shown in table 1.

Table 1. Epidemiological and clinical characteristics of 31 patients.

P	A	S	Type of protein ep and iep	M. Ig type	Proteins Level (g/l)	Protein fractions levels (g/L):					ESR (mm)		Levels of:			
						Al	A1	A2	B	G	FH	SH	CRP (mg/l)	Hg (g/dl)	β 2m (mg/l)	Ca (mmol/l)
1	45	M	ser prot	IgM/K	90	33.12	3.96	8.82	29.52	14.58	NP	NP	NP	NP	NP	NP

2	55	M	ser prot	IgG/L	80	40.64	2.65	10.08	11.84	14.88	10	22	<6	14.6	1.56	2.35
3	60	F	ser prot	IgM/K	110	41.25	2.86	8.8	8.47	48.62	NP	NP	NP	NP	1.31	NP
4	46	F	ur prot	LLC	0.4	-	-	-	-	-	NP	NP	NP	NP	NP	NP
5	57	M	ser prot	IgA/K	76	37.012	2.356	7.524	23.408	5.7	NP	NP	NP	NP	NP	NP
6	59	F	ser prot	IgG/K	106	NF	NF	NF	NF	NF	NP	NP	NP	NP	NP	NP
7	50	F	ser prot	IgG/L	84	38,163	2.772	9.072	8.148	25.878	64	105	NP	12.8	1.05	2.24
8	71	M	ser prot	IgG/L	80	23.2	4.16	14.88	3.68	34.08	NP	NP	NP	NP	NP	NP
9	56	F	ser prot	IgG/L	84	39.06	2.856	9.576	8.232	24.276	26	54	NP	11.6	NP	NP
10	61	F	ser prot	IgG/L	120	30.72	2.4	6.96	5.28	74.64	NP	NP	NP	NP	NP	NP
11	NF	M	ser prot	IgG/L	120	34.92	2.88	7.56	6.96	67.68	NP	NP	NP	NP	NP	NP
12	52	M	ur prot	IgG/K	2	-	-	-	-	-	NP	NP	NP	NP	NP	NP
13	56	M	ser prot	IgA/L	80	36.24	3.12	12.88	13.04	14.72	8	18	<6	11.5	1.56	2.3
14	50	F	ser prot	IgA/K	116	29	1.6	5.68	3.9	74	NP	NP	NP	NP	7.76	NP
15	63	F	ser prot	LLC	72	36.43	3.24	12.96	11.304	8.064	NP	NP	<6	12.4	NP	2.54
16	72	F	ur prot	KLC	1.85	-	-	-	-	-						
			ser prot	KLC	70	35.42	3.08	13.44	9.31	8.75	42	80	<6	NP	14.16	NP
17	49	M	ser prot	IgG/K	94	36.472	3.478	10.81	9.776	33.464	NP	NP	NP	NP	NP	NP
18	67	F	ser prot	IgA/L	120	29.64	3.12	4.44	80.04	2.76	NP	NP	NP	NP	7.98	NP
19	71	M	ser prot	LLC	58	32.712	3.306	7.424	9.744	4.814	NP	NP	NP	7.9	NP	NP
20	54	F	ser prot	IgA/K	110	26.29	2.09	7.04	9.13	65.45	NP	NP	NP	6.4	2.25	NP
21	45	M	ser prot	IgA/L	90	41.58	3.42	10.89	9.45	24.66	NP	NP	NP	NP	NP	NP
22	66	F	ser prot	IgM/K	74	30.118	2.738	7.844	19.092	14.208	NP	NP	NP	NP	NP	NP
23	30	F	ser prot	IgG/K	102	31.212	2.652	6.834	8.772	52.53	NP	NP	NP	10.8	NP	NP
24	58	M	ser prot	IgG/K	80	31.28	4.08	9.2	8.72	26.72	81	115	NP	10.8	NP	NP
25	45	F	ser prot	IgA/K	72	37.152	2.52	7.92	9	15.408	105	132	NP	9.6	NP	NP
26	51	F	ser prot	IgG/L	74	33.152	2.738	9.102	8.51	20.498	64	105	NP	12.3	1.05	2.24
27	59	M	ser prot	IgA/K	96	35.424	2.016	6.528	49.344	2.688	NP	NP	NP	NP	6.77	2.65
28	44	F	ser prot	IgG/K	106	29.468	3.922	12.508	6.996	53.106	NP	NP	NP	NP	NP	2.92
29	57	M	ser prot	IgG/L	70	30.87	4.2	12.11	9.94	12.88	10	22	<6	14.2	1.56	2.35
30	66	F	ser prot	IgA/K	84	33.768	2.268	8.4	31.08	8.484	NP	NP	NP	NP	1.07	NP
31	26	M	ser prot	IgA/K	121	NF	NF	NF	NF	NF	NP	NP	NP	NP	NP	NP

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P: patient; A: age; S: sex; Ep: electrophoresis; IEP: immuno- electrophoresis; M: monoclonal; Ig: immunoglobulin; Al: albumin; A1: alpha 1; A2: alpha 2; B: beta; G: gamma; ESR: Erythrocyte sedimentation rate; FH: first hour; SH: second hour; CRP: C-reactive protein ; Hg: Hemoglobin; β2m: β2-microglobulin; Ca: serum calcium; Ser prot: serum protein; Ur prot: urine protein; M: male; F: female; K: kappa; L: Lambda; LLC: Lambda light chain; KLC: Kappa light chain; NP: not performed; NF: not found.

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3.1. Epidemiological data

The mean age was 54.7 ± 10.7 years with extremes ranging from 26 to 72 years. Fifty-five percent of the patients were female and forty-five were male with a sex ratio 0.82. Statistical analysis of these values by chi square test showed that the results were significant ($\alpha=0.05$).

The two third of our study population were located in the range between 40 and 60 years with equality of reaching for both sexes. However, a female predominance in patients over 60 years was observed (Fig. 1). Results were statistically significant ($\alpha=0.05$). It's noteworthy to mention that data about the age of one patient had not been found.

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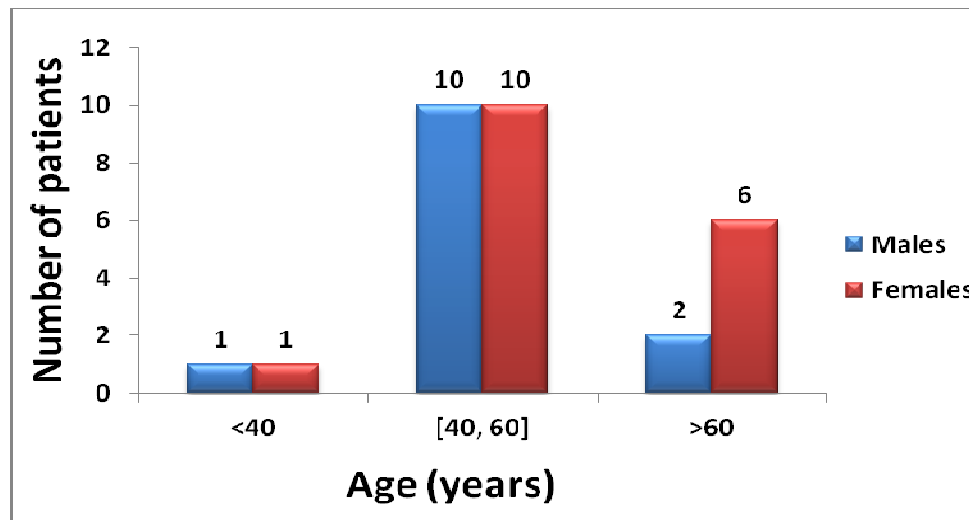


Fig. 1: Distribution of patients according to age and sex (n=30).

3.2. Immunochemical data

According to the electrophoresis results, 66.67% of patients had a gamma globulin monoclonal peak, against 33.33% had a monoclonal peak in beta globulin zone.

The data of immuno-electrophoresis confirmed that the tested population under study had a monoclonal band in serum. In fact, we found that immunoglobulin G monoclonal antibody (Ig G) was placed in the forefront. It was observed in 15 patients (48%), Ig A was found in the second place with 9 cases (29%) followed by 4 of patients (13%), who had free light-chains and 3 patients (10%) had Ig M, while in none of them Ig D and Ig E were detected (Fig. 2).

Besides that, 17 of the patients (55 %) were Kappa-chain positive and 14 (45 %) were Lambda-chain positive.

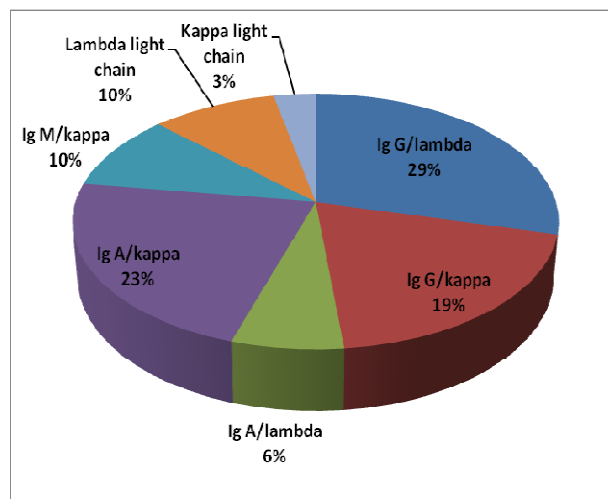


Fig. 2: Percentage of different immunoglobulin subtypes of monoclonal plasmaproliferative disorders (n=31).

3.3. Biological data

In some patients, prognostic factors as ESR, CRP, serum levels of calcium, β 2-microglobulin, hemoglobin and other proteins, were also taken into consideration. According the data of the table 2, the majority of patients didn't follow up the progression of their malignant disorders by biological tests.

Nevertheless, patients requesting for these analyzes demonstrated an acceleration of ESR (66.66% of cases), anemia (50% of cases), an increase in serum level of calcium (37.5% of cases) and β 2-microglobulin serum level was greater than 2.4 mg/l (33.33% of cases). Moreover, the median concentration of proteins was 91 g/l ranged in values varying from 58 to 121 g/l (normal values of serum proteins are between 60 and 80 g/l). It was noted that serum protein electrophoresis had been performed only for 29 patients while the others had urine electrophoresis. Thus, we found that 58.62 % of patients had a hyperproteinemia against 37.93% having normal levels of serum proteins, whereas 3.45 % of cases having a hypoproteinemia, corresponding to a patient with a monoclonal light Lambda chain.

With respect to the spike size, 44.44 % of the cases were below 30 g/l and 55.56 % were above 30 g/l. The median concentration of the monoclonal component was 37 g/l. While, the average level of albumin was 33.86 g/l with extremes ranging from 23.2 g/l and 41.58 g/l.

In seventeen patients (62.96%) having low levels of albumin, 15 patients had higher serum monoclonal protein levels. The remaining two patients had normal concentrations of beta or gamma globulin fractions and were associated with light chain MG.

153 **Table 2. Number and percentage of patients requesting for prognostic analyzes.**

Prognosis factor	Erythrocyte serum rate	CRP	Level of:		
			Calcium	β 2- microglobulin	Hemoglobin
Number of patients who requested for each analysis divided by total number of the studied population (%)	9/31 (29%)	5/31 (16.13%)	8/31 (25.80%)	12/31 (38.70%)	12/31 (38.70%)
Number of patients having anomalies in analysis divided by number of patients requesting for prognostic factors (%).	6/9 (66.66%)	0/5 (0%)	3/8 (37.5%)	4/12 (33.33%)	6/12 (50%)

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155 **4. Discussion**

156 The presented investigation was the first study conducted in 2006 at Pasteur Institute in Casablanca
157 (Morocco) aimed to highlight the epidemiological and biological features of thirty one patients having
158 the risk to develop plasma cell dyscrasias.

159 In this period, there were only five immunochemistry laboratories in Casablanca which performed
160 electrophoresis and immuno-electrophoresis. Among them, figures Pasteur Institute covering not only
161 50% of Casablanca population but also 20% of the population of other four Moroccan cities (Settat,
162 Jadida, Mohammedia and Berrechid).

163 Few years later, many studies, have been performed in Morocco and other countries, were directed to
164 the same target. Some of the results from those studies were consistent with our data, but others were
165 different. In fact, our patients were younger (54.7 years) comparing with what was reported by other
166 surveys. Beginning with a Moroccan investigation which had been executed in Mohamed V Military
167 Hospital of Rabat (2012) [6], the median age was 60.21 years. In other countries, the average age
168 was a bit closer to that found by Moroccan institutions. For instance, in India [7], Egypt [1], Tunisia [8]
169 Lebanon [9] and Saudi Arabia [10], it was 56, 58.5, 62.7, 65 and 65.6 years, respectively. However, it
170 was much higher in Western nations especially in Iceland [11], Spain [12] and France [13] with mean
171 ages of 70, 73 and 79 years, respectively. The observed difference concerning mean ages of patients
172 with MG between Eastern and Western nations may be due to the quality of life, health services and
173 medical scientific researches which differ from developed to underdeveloped countries. Ideally, to the
174 best of our knowledge, no epidemiological study has explored the detection of MGUS in Moroccan
175 population and prediction of its progression to myeloma or related malignancy. Such an investigation

could help to prevent development of a benign disease which requires just a close follow-up to a malignant cancer in patients. Consequently, it may be more cost effective and probably could increase life expectancy among patients with MG.

Besides that, our outcomes had demonstrated that 93.34% of our patients were above 40 years old, but it was important to underline that two patients only were the ages 26 and 30 years. These results were corroborated with that presented in inquire carried out by Kassem et al. (2014) [1] who proved that 96% of patients having PCD were of mature age. This confirmed the data from the literature [1, 4, 7, 14, 15]; monoclonal gammopathies such as CLL, MM and MGUS are diseases of older adults.

Like several investigations, we found that the prevalence of MG increased with the age [1, 7, 13, 15, 16, 17]. Nevertheless, the existing difference between these studies and ours was that we noted a slight predominance of female individuals with a sex ratio 0.82 and an equality of reaching for both sexes in patients aged between 40 and 60 years, while other authors found that men were affected more frequently than women by PCD with different sex ratios 1.08 [11], 1.2 [13, 18], 1.24 [9], 1.43 [1, 10], 1.71 [8], 1.94 [14] and 2.3 [6], respectively. Predominance in female individuals can be explained by the influence of geographical distribution of Casablanca population which was presented by 50.7% of females and 49.3% of males according to 2005 and 2006 statistics performed in Casablanca [19].

On the other hand, the most frequent type of immunoglobulin in our study was Ig G. It was found in 48% of patients, followed by Ig A (29%), monoclonal light chains (13%) and the isotype Ig M (10%) which came in the last place. This distribution coincided with that reported by the clinical oncology department of Cairo University (Egypt) [1], not of point of view percentage but order. In this latter inquiry, it was realized that 63.6% of patients had Ig G against 17.5 % with Ig A, while 13.4% had monoclonal light-chains and 5.5% had an Ig M monoclonal band. Nonetheless, our findings were not in concord with those reported by French studies [13]. Effectively, the first investigation was led in internal medicine department of Rennes university hospital [13] which revealed that isotypes repartition was: Ig G (42.8%), Ig M (31.9%), Ig A (8.9%), biclonal gammopathy (9.8%) and monoclonal light chains (6.6%), respectively. Whereas, the second research, conducted in all department of General Hospital of Blois [13], showed that this distribution was Ig G (59.7%), Ig M (27.5%), Ig A (11.8%) and monoclonal light chains (2.7%), respectively. In contrast, no monoclonal light chain was detected in an Indian investigation [18], while in Singh et al. survey [7], no IgM type paraprotein was observed.

Moreover, electrophoresis showed a monoclonal peak in gamma globulin fraction in 66.67% of the patients. Our findings were in agreement with those previously reported [8, 18, 20] outlining a monoclonal spike in the gamma zone in 78%, 84.8% and 85.5% of cases, respectively. This observation could be explained by the fact that the gamma fraction contains the largest portion of immunoglobulins. Therefore, monoclonal gammopathies are most frequently encountered in this portion of the electrophoresis. Additionally, since most IgG monoclonal proteins are cationic, they migrate to the gamma zone of the electrophoretic gel [21]. This statement may justify the predominance of the isotype Ig G in all the studies discussed above.

In addition, the association of the Ig G with the lambda light chain was established in 29% of cases. In the opposite, the study of Dasse et al. [22] conducted in Abidjan (Ivory Coast) indicating that the association Ig G/kappa was the most found monoclonal form in 60 % of cases.

Alternatively, analysis of the association between heavy and light chains revealed that kappa light chain was more linked than was lambda light chain (55% against 45%, respectively). This statement joined the outcomes of many researches [1, 7, 20, 22].

In this series of 31 patients, all the detected heavy chains were associated to light chains in monoclonal gammopathy (intact immunoglobulin). This was compatible with the data presented by Dasse et al. (2000) [22]. Nevertheless, the presence of immunoglobulin free light chains had been proven in 13 % of cases.

With respect to biological tests, the hyperproteinemia touched 58.62 % of our patients. A similar result was obtained from the study of Gaougaou et al. [23] by noticing an increase of serum protein levels in 63% of cases with MM. It was pointed out that PCDs were not always related with hyperproteinemia. Indeed, it was observed, in the present investigation, cases having free light chains MG and presenting a hypoproteinemia or normal levels of serum proteins. A similar finding was described in another study [21] reporting that the mean serum total protein concentration was significantly higher in IgG, IgA, and IgM compared with free light chain monoclonal gammopathies, where this value was within normal limits. This could be explained by the effect of low molecular weight of the light-chain secreted by malignant plasma cells about 22500 Dalton versus 40000 to 70000 Dalton which shows the variation of molecular weight of the heavy chains. It was important to mention that 17 of 21 patients (80.95%), having total protein level above or equals to 80 g/l, had monoclonal paraprotein concentration above 20 g/l. As was previously reported, in van Hoeven et al., investigation [21], monoclonal proteins often increase serum total protein level. In fact, it was found that paraprotein levels were reflected in significantly increased mean serum total protein in IgG, IgA, and IgM [21].

It was noted as well an increase in β 2-microglobulin in 33.33% of cases. It was already reported that β 2-m is a small membrane protein associated with the heavy chains of class I major histocompatibility complex proteins. It is probably secreted by cancer cells and it's a powerful prognosis factor in correlation with the survival in monoclonal disorders by reflecting the tumor mass [24]. Indeed, according to Di Giovanni et al., [25] in the group of patients suffering from MM or WM, the mean β 2-m level was significantly higher than in the group with MGUS. Values above 3 mg/L were highly indicative of a neoplastic process. They were observed in all the Waldenström macroglobulinemia patients and in greater than 90% of myeloma patients. Another study added that a serum β 2-m level higher than 2.5 mg/L was associated with an increased probability of the risk of asymptomatic MM progression to symptomatic disease along with bone marrow plasma cells and serum or urinary monoclonal component [26]. Furthermore, other investigations showed that 90% and 96.5% of patients with monoclonal gammopathies had high levels of β 2-m, respectively [27, 18]. It was noticed, in the current study, that the patients having β 2-m concentrations above 5.5 mg/l, had albumin levels below or equals to 35 g/l. This finding is in keeping with a previous investigation [28] demonstrating

that serum β 2m values had a negative correlation with serum albumin. These patients had as well serum levels of monoclonal protein above 30 g/l except for one patients suffering from kappa light chain MG. Our data were in concordance with those recorded by Charafeddine et al., [9] demonstrating that β 2-m and albumin were related to spike size. This correlation could be explained by the fact that β 2-m reflects the tumor mass which is detected by hyperproteinemia due to the elevation of serum monoclonal protein in beta or gamma globulin zone. This increase leads often to the decrease of others fractions levels such as serum albumin. Certainly, the increase in monoclonal spike size is in correlation with tumor burden in bone marrow and therefore entails a worse prognosis [9]. Additionally, it was previously described that the concentration of the serum monoclonal protein at diagnosis and the serum albumin value were independent predictors of progression from MGUS to lymphoma or a related disorder with a multivariate analysis [20]. On the contrary, hypoproteinemia or normal levels of proteins were associated with normal concentrations of beta or gamma globulin fractions in patients suffering from light chains MG and presenting high levels of β 2-m and low values of serum albumin concentrations. This result joined that reported by Charafeddine et al., [9] finding that most of the patients diagnosed to have light chain MG had a spike size below or equals to 20 g/l. Thus, the association of albumin and β 2-m serum levels could be good prognosis factors to detect PCDs. This statement proves that electrophoresis and immnuo-electrophoresis aren't sufficient tools to lead a MG diagnosis which requires performing biological tests and biopsy. These results have to be proven by statistical analysis by investigating the involvement of both β 2-m and albumin serum levels in MG prognosis in a large-scale of Moroccan patients.

With regard to serum calcium levels, according to the results of the current study 37.5% of the patients had hyper-calcemia leading to the risk of bone lesions and collapse of the vertebral body. This was supported by the deduction reached by Pagano and collaborators [27] who noticed that 27% of patients suffering from plasma cell leukemia had an elevation in serum calcium level. Hyper-calcemia is one of important factors besides renal insufficiency, anemia, and lytic bone lesions (CRAB criteria), that can distinguish between MM and MGUS [1, 29, 30], since patients with the premalignant plasma cell disorder are known by absence of hyper-calcemia [20]. However, because MGUS is a condition of the elderly, concomitant diseases can confound the distinction [31]. For instance, hypercalcemia may be caused by hyperparathyroidism that should be considered in the absence of skeletal lesions [31]. It was also made out in the present investigation, that the patients having hyper-calcemia had high values of β 2-m serum concentrations, albumin levels below or equals to 35 g/l and serum levels of monoclonal protein above 30 g/l except for one patients suffering from kappa light chain MG. As was discussed above, high concentrations of calcemia could be considered as a prognostic factor of PCDs as well as of β 2-m and albumin serum levels.

It was also established that the emergence of anemia was more thrust. It was perceived that 50% of patients had a drop in rate of hemoglobin which may reveal the impact of the plasma cell infiltration on the bone marrow production. In other surveys [7, 27, 18], anemia features were also detected, but only in 48%, 25%, and 7.2% of patients, respectively. It should be noticed that our six patients having anemia might not be affected by solitary plasmacytoma. In fact, the decrease of serum hemoglobin

level isn't a criterion of this disease which is also characterized by a low serum or urinary level of monoclonal immunoglobulin [32]. In contrast, these patients could have MM or WM for which anemia is a common complication [4]. In the current study, it was also observed that 4 of 6 patients with anemia had albumin levels below 35 g/l but had variable levels of serum monoclonal paraprotein (below or above 30 g/l regardless of the immunoglobulin isotype). Various studies had demonstrated a positive correlation between hemoglobin and albumin levels in patients with MG [9, 17]. However, according to our study the two factors under discussion may not be indicators of the increase of monoclonal component (MC) levels of non IgM MG. In fact, as was previously reported [20, 31], anemia may be multi-factorial in the elderly. It could be caused by conditions other than MG such as renal insufficiency, iron deficiency, nutritional imbalance, occult gastrointestinal bleeding, or, less frequently, myelodysplastic syndrome. On the other hand, our observation didn't corroborate with that described by Charafeddine et al., [9] investigation carried out in the clinical laboratory of the American University of Beirut Medical Center for 540 patients. It was reported that low serum concentrations of hemoglobin and albumin showed significant correlation with high M spike size above 20 g/l. The difference between the two inquiries resides in the size of the population under study. Thus, our outcome should be confirmed or rejected after studying the impact of prognostic factors in a large number of patients.

Furthermore, it was explored that 66% of our patients had a higher erythrocyte sedimentation rate (ESR). In others surveys, an elevation of this biological test was observed in all seven reported cases with plasma cell leukemia [33] and in 94.6%, 17.9%, 25.5% of patients with MM [23], MGUS and SMM [34], respectively. In the present study, whatever were the ESR levels, MC concentrations were lower than 30g/L. Probably; there is no clear relationship between ESR levels and the size of MC in patients with MG as was previously reported [34], suggesting variability in the interaction of individual MCs with red cells to create rouleaux formation [34]. Besides, we cannot judge whether or not ERS is a prognostic factor of PCDs due to the small number of patients followed-up.

Unlike the study, performed by Salonen and Nikoskelainen [35], displaying elevated CRP levels in patients with hematological malignancies (around 152 mg/l), all our five patients had a normal CRP, a prognosis index, correlated with survival and activity of proliferative cells [24]. It is also an infection indicator as a cause of death in patients with PCDs [35]. Despite of this positive outcome, the majority of serological and hematological examinations allowing to patients to have a rigorous monitoring of their MG, had not been carried out by all of them. Additionally, the differential diagnosis between different disorders may not be done. Effectively, findings of Ig M MG, plasma cell proliferation on bone marrow biopsy and clinical findings consistent with myeloma (CRAB signs) classically distinguished the rare diagnosis of Ig M MM from the more common WM characterized with a monoclonal Ig M and known by lymphadenopathy, organomegaly, lymphoplasmacytic lymphoma and hyper-viscosity (related to the absolute level and structure of the Ig M pentamer) [29]. Conversely, some patients may not have all of these findings. Both diseases could share clinical and biological manifestations such as hyper-viscosity which may lead to diagnostic errors [29, 36, 37]. Recent advances in cytogenetic and immuno-phenotyping of bone marrow plasma cells can help further define the differences between

IgM MM and WM [29, 38]. Myeloma plasma cells lack CD19, CD45, and CD27 expressions and are positive for CD56 (75%), CD117 (30%), and CD20 (30%) according to the report of Rawstrom et al. (2008) [39], while in WM, clonal B-cells express CD19, CD20, CD45 [37]. Similarly, MM is characterized, in contrast to WM, by chromosome translocations which include not only the t(11;14) but also the t(4;14) and t(14;16) located in the genes coding for immunoglobulin heavy chains [38].

It was noteworthy that without having results of bone marrow biopsy and the lack of performing biological examinations in the current study, the type of MG couldn't be determined. Moreover, electrophoresis and immuno-electrophoresis assays could predict MG affection but they should not be considered sufficient testing when contemplating a diagnosis of a PCD [40]. For this reason, the diagnostic of each disorder requires making bone marrow biopsy to confirm diagnosis with clinical, radiologic studies and laboratory tests.

Importantly, a definitive diagnostic allows the choice of the adequate treatment for each PCD by taking in consideration age, gender, race, family history.

Our study had several limitations; the laboratory data of the MG cases were included without their clinical diagnosis and many factors affecting prognosis were not assessed in the univariate and multivariate analyses due to the limited number of patients. Moreover, the current study was Pasteur Institute based and thus cannot be generalized for the entire Moroccan population.

5. Conclusion

The purpose of the current study was to evaluate epidemiological and biological characteristics of patients with monoclonal gammopathies detected by the association of electrophoresis and immuno-electrophoresis. Our data were very similar to those reported by others investigations but slightly different in the aspect of mean age and sex ratio. It is also important to mention that biological tests weren't performed by all members of our cohort, probably because of financial constraints, that limit the opportunity for monitoring of their disorders progression and response to the respective treatment.

Ethical approval

Ethical committee of Pasteur Institute of Casablanca Morocco approved the study.

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