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– ORIGINAL PAPERS –

IgA Myeloma at Diagnosis – Clinical, Paraclinical Characteristics and Response to First Line of Treatment

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Abstract

Objectives*: Real-life data on IgA-secretory multiple myeloma tends to suggest a more unfavorable prognosis due to its aggressive nature and clinical features, without clear arguments in favor of this theory in literature. In this paper our aim was to collect clinical and paraclinical features at diagnosis and to evaluate the response to the first line of treatment in a cohort of patients from our clinic.*

Material and methods: *A retrospective study on a cohort of 32 patients diagnosed at the Hematology Clinic of Colțea Clinical Hospital between 2021-2023. Clinical and biological data that were selected at diagnosis for descriptive analysis include: age, sex, complete blood count, inflammatory markers, beta2 microglobulin, plasma cell infiltrate, serum creatinine, serum total protein, serum calcium, albumin, monoclonal protein, extramedullary disease and response to first-line of therapy.*

Outcomes: *The median age at diagnosis was 62 years. One-third (34.3%) of patients presented with hypercalcemia (≥11 mg/dl) and 25% of patients had renal impairment according to the diagnostic criteria. A significant percentage of patients (43.75%) had bone implication at diagnosis. Regarding response to first-line therapy, 50% did not meet the response criteria (considered as complete response, very good partial response or partial response). Proinflammatory status of patients (particularly erythrocyte sedimentation rate (ESR) >115 mm/h) was found to be statistically correlated with response. Other factors that were found to have a negative impact on treatment response were: age≥65 years, lactate dehydrogenase (LDH) > upper limit of normal (ULN) and serum creatinine ≥2 mg/dl. High values of beta2-microglobulin (b2M) proved to be statistically correlated with pathologic bone fractures.*

Conclusions: *IgA-secretory myeloma comprises a low incidence subcategory of myeloma characterized by a high percentage of extramedullary disease and bone lesions. The proinflammatory microenvironment is a central element in myeloma pathology. The majority of the patients in the cohort (80%) presented with hyperviscosity, and we demonstrated a direct proportional relationship between ESR, C-reactive protein (CRP) and b2M. In the present study there was a correlation between the value of beta2-microglobulin and pathologic bone fractures. Another central element in the pathogenesis of MM is immunosuppression, which we confirmed in this study by the presence of low IgG values (91%).*

Keywords: *IgA multiple myeloma, prognostic factors, beta-2 microglobulin, first line therapy, erythrocyte sedimentation rate*

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Introduction

Multiple myeloma is a complex malignant plasma-cell proliferative disease that is often accompanied by the secretion of monoclonal immunoglobulins and multivisceral implications. It is the second most common hematological malignancy in Europe and the third most common in Romania according to the Global Cancer Observatory (GLOBOCAN) 2022 data.[1,2] The main characteristic of monoclonal gammopathies is determined by proliferation of a single B-cell malignant clone, resulting in a monoclonal population of immunoglobulins[3]. The malignant plasmacytic clone has the role of suppressing the secretory activity of other immunoglobulins, thus two thirds of patients present with antibody deficits. Infiltration of malignant plasma cells in the bone marrow induces a functional myelosuppression with appearance of anemia associated or not with leukopenia and thrombocytopenia, infiltration of bony structures with characteristic lesions, production and secretion of monoclonal component with impairment of normal immunity and consequential susceptibility to infections. Even though IgA-secretory multiple myeloma is the second most common type of multiple myeloma after IgG type, the characteristics of the IgA plasma cell neoplasms are not clearly reported in the literature. Studies suggest that IgA-secretory myeloma is a low incidence subcategory of myeloma characterized by a high percentage of extramedullary disease and bone lesions[4]. Regardless of clear arguments in favor of this theory in literature, real-life data supports the idea that IgA-secretory myelomas have an unfavorable prognosis due to its aggressive nature and clinical features[5].

Objectives

The main goal of this study is to examine IgA plasma cell neoplasms within our center. Our objectives were to identify the epidemiologic, clinical, paraclinical features at diagnosis, therapeutic and evolutionary aspects of IgA-secretory MM patients and to observe factors associated with response to first line of treatment and overall outcomes.

Patients and method

This was a retrospective, descriptive and analytical study conducted in Colțea Clinical Hospital, Hematology Clinic. The study included 32 patients, diagnosed with IgA multiple myeloma between January 1, 2021 and December 31, 2023. For diagnosis The International Myeloma Working Group (IMWG) criteria were used.[3] To diagnose multiple myeloma the following criteria must be met, such as clonal bone marrow plasma cells ≥ 10% or a biopsy-proven osseous or extramedullary plasmacytoma and at least one myeloma defining event. A myeloma defining events is characterized by CRAB features which is translated in hypercalcemia, renal failure, anemia, or bone lesions, as well as three specific biomarkers: clonal bone marrow plasma cells ≥ 60%, serum free light chain ratio ≥100, and more than one focal lesion on magnetic resonance imaging (MRI)[6,7]. For staging the patients' disease, The International Staging System (ISS) classification was used[7]. Response to first line of treatment was analyzed using the IMWG response criteria and taking into consideration the overall response rate, which included a partial response, a very good partial response and a complete response[8].

Clinical and biological data that were selected at diagnosis for descriptive analysis and that were analyzed for their effect on the primary endpoint (response to first line treatment) include: age (<65 vs. ≥65 years), sex (male vs. female), neutrophil count (>2.2 vs. ≤2.2 mm3), hemoglobin value (<8.5 vs 8.5-10 vs ≥10.0g/dL), inflammatory markers such as ferritin (<1000 vs. ≥1000 ng/ml), ESR (40-99 vs. 100-114 vs. ≥115mm/h) and CRP (1 vs. ≥1 mg/dl), b2M (<3.5 vs 3.5-5.5 vs ≥5 mg/dl), plasma cell infiltrate (<60 vs. ≥60%), serum creatinine (<2 vs. ≥2 mg/dl), urea (<40 vs. ≥40 mg/dl), serum total protein (<8 vs. ≥8g/dl), total serum calcium (<11 vs. ≥11 mg/dl), serum albumin (<3.5 vs. ≥3.5g/dl), level of monoclonal protein, presence of extramedullary disease, first-line treatment and response to first-line of therapy. For statistical analysis we used univariate and multivariate analysis to determine the correlations between multiple aspects of the disease and response to first-line of treatment with a $P \leq 0.05$ being considered statistically significant.

Results

A number of 32 patients were included in our analysis. The median age of the cohort was 62 years and the sex ratio was 1.28 (F/M). The most common symptom at diagnosis was bone pain (n= 20; 62,5%). Fourteen patients (43,8%) presented with bone manifestations at onset, such as plasmacytomas (n=6; 18,8%) and pathologic bone fractures (n=8; 25%). Eighteen patients (56.25%) were diagnosed with stage III myeloma, seven patients (21,8%) with stage II and the other seven patients were diagnosed with stage I multiple myeloma according to ISS classification. One patient had a fulminant

evolution to plasma cell leukemia (PCL). Anemia was present in 62,5% of cases, of which 34,5% presenting with severe anemia (Hb<8g/dl). The severity of anemia was both correlated with the percentage of bone marrow plasma cells (p=0.001) and serum creatinine levels (p=0.033). A detailed overview of the descriptive analysis can be found in Table no. 1.

	no	%		no	%
Sex			**Age (years)**		
Female	18	56	<65	18	56
Male	14	44	≥65	14	44
Neutrophil count (microl)			**IgA (mg/dl)**		
≤2.2	6	18.8	<3000	15	46.8
>2.2	26	81.2	>3000	17	53.2
Hemoglobin (g/dl)			**IgG (mg/dl)**		
<8.5	11	34.5	<700	29	91
8.5-10	9	28	>700	3	9
>10	12	37.5			
ESR (mm/h)			**LDH (U/L)**		
≤99	7	22	≤246	21	65.6
100-115	10	31	>246	11	34.4
>115	15	47			
Plasma cells count (%)			**Light chains**		
<60	20	62.5	Kappa	21	65.6
>60	12	37.5	Lambda	11	34.4
Serum total protein (g/dl)			**Creatinine (mg/dl)**		
≤8	8	25	≤2	27	84.4
>8	24	75	>2	5	15.6
Serum calcium (mg/dl)			**CrCl (ml/min)**		
<11	21	65.6	≤40	8	25
≥11	11	34.4	>40	24	75
Serum albumin (g/dl)			**B2microglobulin (mg/l)**		
<3.5	10	31.2	<3.5	8	25
≥3.5	22	68.8	3.5-5.5	6	18.8
			>5.5	18	56.2
Bone lesions			**Treatment response**		
Plasmacytomas	6	18.8	Yes	16	50
Bone fractures/osteolysis	8	25	No	16	50
First-line treatment					
CyBorD	19	59,3			
Vel/Dex	4	12,5			
DVMP	1	3,1			
DVTD	4	12,5			
DRd	2	6,25			
VRd	2	6,25			

Table 1.

The proinflammatory microenvironment is a central element in myeloma pathology. We identified a strong direct correlation between the values of the ESR, CRP, beta2-microglobulin and the rate of response to first-line treatment in the presented group. Amongst the three, ESR seems to have the most extensive statistical impact on treatment response. Twenty-five (78%) patients presented with ESR values ≥100mm/h with 47% of patients having an ESR of ≥115mm/h, found to be a cut-off value with statistically significant prediction for lack of response to treatment (p=0.042). ESR was also statistically correlated with the percentage of medullary plasma cells (p=0.005) and the level of IgA monoclonal protein (p=0.006).

When analyzing through linear regression different potential predictors, ESR was the only identified predictive factor to first-line treatment response. We then used different combinations of potential predictors in hope of identifying a predictive model for treatment response. When separating the patients in different categories by using cut-off values on the predictors (a detailed description can be found above in the methodology and Table 1), the strongest predictive model

for treatment response was found to be one that included four predictive factors: ESR ≥115 mm/h, age≥65 years, lactate dehydrogenase >ULN and serum creatinine ≥2 mg/dl (p=0,002). Interestingly, the most important negative predictor of treatment response was found to be serum creatinine (p=0.048). When removing it from the analysis, the predictive model remained statistically significant but lost a large amount of its statistical power (p=0.023).

Almost one third of patients (37,5%) presented with a number of >60% plasma cells in the bone marrow at diagnosis. 34.4% of patients had hypercalcemia ≥11 mg/dl and 25% of patients had renal impairment according to the diagnostic criteria (Cr≥2 mg/dl and/or CrCl≤40 ml/min). An important number of patients in the cohort (n=18; 56,2%) had values >5.5 mg/dl of b2M, where we demonstrated a causal relationship between this biological finding at diagnosis and pathologic bone fractures (p=0.05). Almost all patients (27 of 32) had very high values of monoclonal protein IgA (>5ULN), with concomitant suppression of polyclonal protein secretion, a situation also found in the presented cohort and expressed by low IgG values (<700mg/dl) in 91% of patients, correlated with the infection rate in the analyzed group. 65.6% of patients IgA multiple myeloma had with kappa light chain secretion.

Regarding first-line therapy, all patients received specific treatment. The combination of Cyclophosphamide, Bortezomib and Dexamethasone (CyBorD) was used in 59,37% of cases (n=19). Other protocols used based on specific disease characteristics and patient features were: DVTd (n=4, 12,5%), DRd (n=2, 6,25%), Vel/Dex (n=4, 12,5%), VRd (N=2, 6,25%), DVMP (n=1, 3,1%). In terms of response to first-line therapy, 50% of patients did not meet the response criteria (considered complete response, very good partial response or partial response). Also, during first-line therapy, 60% of patients developed low-grade peripheral neuropathy, which did not require stopping treatment.

Discussions

IgA-secretory multiple myeloma is a low incidence subcategory of plasma-cell malignancies that account for around 21-22% of all multiple myeloma cases[9,10]. Real-life experience brings forth the impression that patients presenting with this subtype of myeloma have poorer long-term outcomes because of lower rates of treatment response and the higher rates of complications presented at diagnosis, but there is no data to support this idea in the literature. As such, in this study we tried to identify different clinical and paraclinical characteristics of IgA-secretory multiple myeloma patients. It is a very well-known fact that the bone marrow microenvironment in MM is characterized by imbalances in the pro inflammatory vs. anti-inflammatory equilibrium. Studies on the bone marrow microenvironment show an increase in the secretion of pro-inflammatory mediators such as interleukins, endothelial growth factor and cytokines, which in turn supports the development of plasma cells by acting as growth factors and creating a medullary microenvironment that promotes MM evolution[11]. Among these mediators, interleukin-6 (IL-6) seems to be a major regulator of these mechanisms and high serum IL-6 concentrations in MM patients has been shown to be associated with poor prognosis[12]. Unfortunately, in our study population data about serum IL-6 levels at diagnosis were limited and as such we turned our attention towards other inflammatory markers that were available, such as ESR, CRP and b2M. The levels of these markers correlated with one another and all three were shown to have an impact on treatment response. Between the three, ESR levels seem to be the most important statistically significant predictive factor, with a cut-off level of 115 mm/h being predictive for poorer outcomes. Also, we identified a correlation between ESR and medullary plasma cells and IgA monoclonal secretion. Given these correlations, we believe ESR to be a very good predictor for disease activity and overall prognosis. Beta2-microglobulin is a well-established predictive marker for tumor burden, response to treatment and long-term prognosis, as is proved by the International Staging System. In one study, levels of b2M correlated with survival prediction, but also with the duration of remission, remaining at low levels during remission and higher levels at the moment of relapse[13]. Tumor burden measurement in MM is difficult and indirect. Some of the indicators that have been proposed for measuring tumor burden include the percentage of medullary plasma cells and the levels of M paraprotein[14]. In our study population we did not validate these proposed factors in relationship with levels of b2M at diagnosis. However, we did find a statistical correlation between the levels of b2M and the severity of anemia (p=0.002). Moreover, we identified a relationship between b2M levels and the presence of pathologic bone fractures (p=0.05). The presence of pathologic bone fractures is suggested to be a factor for poor outcome and lower rates of survival[15]. As such, we believe that b2M in our cohort can be taken into consideration as a predictive factor for the extent of the disease, from the presence of complications at diagnosis which leads to a difficult therapeutic approach which in

turn leads to poorer response rates and survival. One final point that is worth mentioning is that b2M is known to have increased values in kidney disease as a result of renal tubular damage and as such its values are dependent on serum creatinine levels. In our study, b2M correlated with the severity of anemia and the presence of pathologic bone fractures even in patients with normal serum creatinine levels and thus we consider that b2M can be taken into account as a predictive factor regardless of renal function.
The best predictive model for treatment response in our study was one that included ESR ≥115 mm/h, age ≥65 years, LDH ≥ULN and serum creatinine ≥2 mg/dl (p=0,002). We have already discussed about ESR being a good predictor for disease activity and outcome. Age over 65 years is a well-known predictive factor for MM, as a result of more unfavorable features at diagnosis. That was the case with our study group as well, patients over 65 years old presenting higher ISS stages, lower hemoglobin levels or higher values of the inflammatory markers, especially ESR. Another point that has to be taken into account is the higher prevalence of comorbidities in the old age population which can lead to less than ideal therapeutic strategies. Finally, the entire process of human aging is associated with reductions of renal, hepatic and cardiovascular function, which can in turn lead to alterations of the pharmacokinetics of the drugs used and as such reducing the efficacy of the drugs or potentially increasing their toxicity. LDH values above ULN have been identified as a prognostic marker in MM and is used in the Revised International Staging System, being a predictive biomarker for disease aggressiveness, tumor burden (especially extraosseous disease) and potentially resistance to chemotherapy[16,17]. Renal impairment (serum creatinine ≥2 mg/dl) has been identified as a negative prognostic factor on survival in patients with newly diagnosed MM[18,19]. The extent of kidney disease in gammopathies is well studied, to the extent of bringing forward newer entities such as monoclonal gammopathy of renal significance[20]. Renal impairment in MM can be the result of physiological old age reduction of its function, presence of comorbidities or the consequence of secretion of M protein by the plasma cells. Its impact on response to first-line therapy might be the result of non-use of drugs because of the impairment (e.g. avoiding the usage of immunomodulators in severe renal impairment). If we take into consideration all the factors in this predictive model, it seems that they are all interconnected by two elements: higher disease activity and more difficult therapeutic approaches.
Response rates to first line treatment in our study was 50% (n=16/32). As we discussed above, there are some potential predictive factors that can be accounted for this poor response rate in IgA-secretory myelomas, although it is not very clear to which extent each of these factors have an impact on treatment response. One limitation of this study is the presence of a small cohort for analysis. Another limitation is the fact that we had no direct comparison data between our cohort and other IgA-secretory MM cohorts. As such, the comparisons that we drew on are from cohorts that include all subtypes of MM. One future study direction that we plan is the inclusion of an IgG-secretory MM cohort diagnosed in the same period in our Clinic and a direct comparison between the two cohorts in order to understand if the characteristics that we identified in this study differ from those of other subtypes of MM.

Abbreviations list:
MM - multiple myeloma
ESR - erythrocyte sedimentation rate
LDH - lactate dehydrogenase
B2M - beta2-microglobulin
CRP - c-reactive protein
IMWG - the international myeloma working group
MRI - magnetic resonance imaging
ISS - the international staging system
PCL - plasma cell leukemia
IL-6 - interleukin-6

Conflicts of interest
I undersign, certificate that I do not have any financial or personal relationships that might bias the content of this work. The authors declare no conflict of interest

The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

References

1. Ferlay J, Ervik M, Lam F, Laversanne M, Colombet M, Mery L, Piñeros M et al. (2024). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Accessed October 29 (https://gco.iarc.who.int/today)

2. Guilal R, Bendahmane F, Settouti N, Benazzouz A, Chikh A. Clinical and paraclinical factors selection for

multiple myeloma diagnosis. 2019 International Conference on Advanced Electrical Engineering (ICAEE), Algiers, Algeria, 2019, pp. 1-6, doi: 10.1109/ICAEE47123.2019.9014837.

3. Cirlan L, Badelita S, Coriu D. Multiple myeloma and solid tumors - a frequent rarity -. Documenta Haematologica. 2024 Mar. Vol. 2 Issue 1. https://doi.org/10.59854/dhrrh.2024.2.1.27

4. Wang L, Jin FY, Li Y, Sun JN, Zhang JJ, Tang R et al. IgA Type Multiple Myeloma, Clinical Features, and Prognosis. Chin Med J (Engl). 2018; 131(10):1249-1250. doi: 10.4103/0366-6999.231513.

5. Habermehl GK, Nakashima MO, Cotta CV. IgA plasma cell neoplasms are characterized by poorer long-term survival and increased genomic complexity compared to IgG neoplasms. Ann Diagn Pathol. 2020 Feb; 44:151449. doi: 10.1016/j.anndiagpath.2019.

6. Rajkumar SV. Multiple myeloma: 2018 update on diagnosis, risk-stratification, and management. Am J Hematol. 2018; 981–1114. doi:10.1002/ajh.25117.

7. Durie BGM, Salmon SE. A clinical staging system for multiple myeloma correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. Cancer. 1975; 842–854. doi:10.1002/1097-0142(197509)36:3<842::aid cncr2820360303>3.0.co;2-u

8. Durie BG, Harousseau JL, Miguel JS, Bladé J, Barlogie B, Anderson K et al. International Myeloma Working Group. International uniform response criteria for multiple myeloma. Leukemia. 2006 Sep; 20(9):1467-73. doi: 10.1038/sj.leu.2404284.

9. Nair B, Waheed S, Szymonifka J, Shaughnessy JD Jr, Crowley J, Barlogie B. Immunoglobulin isotypes in multiple myeloma: laboratory correlates and prognostic implications in total therapy protocols. Br J Haematol. 2009 Apr; 145(1):134-7. doi: 10.1111/j.1365-2141.2008.07547.

10. Herrinton LJ, Demers PA, Koepsell TD, Weiss NS, Daling JR, Taylor JW et al. Epidemiology of the M-component immunoglobulin types of multiple myeloma. Cancer Causes Control. 1993 Mar; 4(2):83-92. doi: 10.1007/BF00053148.

11. Musolino C, Allegra A, Innao V, Allegra AG, Pioggia G, Gangemi S. Inflammatory and Anti-Inflammatory Equilibrium, Proliferative and Antiproliferative Balance: The Role of Cytokines in Multiple Myeloma. Mediators Inflamm. 2017; 2017:1852517. doi: 10.1155/2017/1852517.

12. Tienhaara A, Pulkki K, Mattila K, Irjala K, Pelliniemi TT. Serum immunoreactive interleukin-6 and C-reactive protein levels in patients with multiple myeloma at diagnosis. Br J Haematol. 1994 Feb; 86(2):391-3. doi: 10.1111/j.1365-2141.1994.tb04748.

13. Bataille R, Grenier J, Sany J. Beta-2-microglobulin in myeloma: optimal use for staging, prognosis, and treatment--a prospective study of 160 patients. Blood. 1984 Feb; 63(2):468-76. PMID: 6362753.

14. Joshua D.E. (2004). Tumor Burden. In: Berenson, J.R. (eds) Biology and Management of Multiple Myeloma. Current Clinical Oncology. Humana Press, Totowa, NJ. https://doi.org/10.1007/978-1-59259-817-5_7

15. Sonmez M, Akagun T, Topbas M, Cobanoglu U, Sonmez B, Yilmaz M et al. Effect of pathologic fractures on survival in multiple myeloma patients: a case control study. J Exp Clin Cancer Res. 2008 Jun; 27(1):11. doi: 10.1186/1756-9966-27-11.

16. Palumbo A, Avet-Loiseau H, Oliva S, Lokhorst HM, Goldschmidt H, Rosinol L et al. Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. J Clin Oncol. 2015 Sep; 33(26):2863-9. doi: 10.1200/JCO.2015.61.2267.

17. Dimopoulos MA, Barlogie B, Smith TL, Alexanian R. High serum lactate dehydrogenase level as a marker for drug resistance and short survival in multiple myeloma. Ann Intern Med. 1991 Dec; 115(12):931-5. doi: 10.7326/0003-4819-115-12-931.

18. Courant M, Orazio S, Monnereau A, Preterre J, Combe C, Rigothier C. Incidence, prognostic impact and clinical outcomes of renal impairment in patients with multiple myeloma: a population-based registry. Nephrol Dial Transplant. 2021 Feb; 36(3):482-490. doi: 10.1093/ndt/gfz211.

19. Chen X, Luo X, Zu Y, Issa HA, Li L, Ye H et al. Severe renal impairment as an adverse prognostic factor for survival in newly diagnosed multiple myeloma patients. J Clin Lab Anal. 2020 Sep; 34(9):e23416. doi: 10.1002/jcla.23416.

20. Zidaru L, Badelita S, Petre N, Coriu D. A Rare Case of Immunotactoid Glomerulopathy Associated with Monoclonal Gammopathy of Renal Significance and Potential Multiorgan Involvement. Documenta Haematologica. 2024 Mar. Vol. 2 Issue 1. https://doi.org/10.59854/dhrrh.2024.2.1.41