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Characteristics of 15 Subjects Affected by IgD Multiple Myeloma and the Key Role of the Laboratory in Diagnosis: A Retrospective Study Report and Literature Review

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Abstract: Immunoglobulin D (IgD) myeloma represents an uncommon subtype of multiple myeloma (MM), accounting for 1–2% of cases. Subjects affected by IgD MM have been demonstrated to have an inferior outcome and survival compared to those with other MM subtypes. A retrospective study was conducted on 15 patients (9 males and 6 females) diagnosed from 2008 to 2022 with IgD MM, in order to investigate the clinical and biochemical features at the moment of diagnosis, cytogenetic alterations, and survival times. The median age was 69 years, and higher frequencies of bone lesions, renal impairments, Bence–Jones proteinuria, and increased serum LDH were observed. Serum calcium levels were in the reference ranges. In the assessment of protein electrophoresis patterns, nine patients had a serum monoclonal protein that was not detectable. A cytogenetic analysis via fluorescence in situ demonstrated that the most common abnormalities were the deletion of 13q and IGH rearrangements. Patients treated with new chemotherapeutic drugs (immunomodulators, proteasome inhibitors), with or without autologous stem cell transplantation presented a higher median survival. The fundamental role of the laboratory in monoclonal IgD detection and the monitoring and studying of IgD MM cases enhances the knowledge of this disease, thus improving patient outcomes.

Keywords: immunoglobulin D; laboratory; multiple myeloma; survival; response therapy; autologous stem cell transplantation; genetic aberration

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1. Introduction

Multiple myeloma (MM) is a neoplastic lymphoproliferative B-cell disease characterized by an overproduction of monoclonal (M) protein and organ damage, including renal failure, hypercalcemia, anemia, and bone lesions [1]. Immunoglobulin (Ig) D multiple myeloma is a rare subtype of MM, accounting for about 1–2% of all cases of MM [2–8]. It was first reported by Rowe and Fahey in 1965 [9]. IgD is found in the serum at a relatively low amount (0–0.1 g/L) compared to IgA, IgG, and IgM, and presents a half-life of 2.8 days, thus determining a very small or even unrecognizable M-spike on protein electrophoresis and protein immunofixation in monoclonal gammopathy cases [2,3,5]. Because of the low number of subjects affected by IgD MM and the paucity of large-scale clinical data, studies on the IgD type of myeloma are limited. IgD myeloma is usually more aggressive, and, like other subtypes of MM, presents bone destruction, amyloidosis, and hypercalcemia but, conversely, a higher incidence of renal insufficiency, Bence–Jones proteinuria, younger age, and genetic abnormalities when compared with other myelomas [2,6,8]. The subjects affected by IgD myeloma present a poorer prognosis and inferior outcomes when compared

to other subtypes. However, the recent progress in therapies increased the response to treatment and prolonged the survival of patients with IgD [2,3,5]. Here, we performed a retrospective analysis of the clinical features, cytogenetic abnormalities, and survival of 15 cases diagnosed as affected by IgD MM at the Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy, between 2008 and 2022, with the aim to observe the improvements in the treatments and outcomes and a better comprehension of this rare pathology.

2. Materials and Methods

2.1. Patients

A retrospective analysis was performed of 15 patients admitted to the San Gerardo Hospital, Monza, Italy, from 2008 to 2022, who were diagnosed with IgD MM using the International Myeloma Working Group (IMWG) diagnostic criteria [10]. The patients were staged following the stratification algorithm Revised International Staging System [11].

2.2. Definition of Response

The IMWG established the criteria for assessing clinical responses in subjects affected by multiple myeloma: (I) a complete response (CR); (II) a very good partial response (VGPR); and (III) a partial response (PR). A progressive disease was defined as an increase greater than 25% from the lowest response value in one or more of the following parameters: serum M-protein ($\geq$0.5 g/dL), urine M-protein ($\geq$200 mg/24 h), bone marrow plasma cell percentage (>10%), development of new bone lesions, and development of hypercalcemia (>11.5 mg/dL). A disease that did not meet the criteria for PR, VGPR, CR, or progressive disease was defined as a stable disease (SD) [12]. Overall survival (OS) was calculated starting from the date of the first treatment to the date of death or the date the patient was known to be alive. For the analysis of OS, the population study was divided into two groups: one group received chemotherapy treatments (named non-transplant group), and the other group was treated with chemotherapeutic drugs followed by autologous stem cell transplantation (ASCT) (named transplant group). For the analysis of the association between the type of treatment and OS, the population study was divided into three groups: the first group received conventional chemotherapy treatment, the second group was treated with new chemotherapeutic drugs (bortezomib–melphalan–prednisone (VMP), bortezomib plus dexamethasone (VD), lenalidomide plus dexamethasone (RD), bortezomib–lenalidomide–dexamethasone (VRD), and VD regimen plus thalidomide (VTD)), and the third group included subjects who received conventional or new chemotherapeutic drugs followed by ASCT.

2.3. Statistical Analysis

Statistical analyses were performed using MedCalc for Windows, version 19.4 (MedCalc Software, Ostend, Belgium). Categorical variables were expressed as counts, percentages, and medians, and compared using the Chi-square test or Fisher's exact p-test. A p value < 0.05 was considered statistically significant.

3. Results

Fifteen patients diagnosed with IgD multiple myeloma using clinical findings (bone marrow biopsy, X-ray, and computed tomography), serum immunofixation, and laboratory data, which accounts for about 1% of all cases of MM detected in our hospital, were retrospectively enrolled in this study. Table 1 describes the baseline laboratory and clinical characteristics of all subjects at the time of diagnosis. The median age of the patients was 69 years (range of 52–83) with a higher frequency of males (9/15, 60%). Bone lesions were detected in nine cases (60%) and anemia in seven cases (47%). Serum calcium levels were within normal reference ranges in all subjects (8.5–10.3 mg/dL), while serum lactate dehydrogenase (LDH) presented high values (>214 U/L, reference range: 135–225 U/L) in nine cases (60%). Seven patients (47%) had renal impairment with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2. Nine patients (60%) had a serum monoclonal

protein not detectable in serum protein electrophoresis. Twelve patients had λα light chains (80%) and only three κ light chains (20%). Bence–Jones proteinuria was detected in 11 patients (73%).

Table 1. Baseline patient characteristics (n = 15).

Male/female		9/6
Median age at diagnosis (year)		69 (range 52–83) ≤65 = 6 (40%), >65 = 9 (60%)
Light chain type		
	κ	3 (20%)
	λ	12 (80%)
Bone marrow infiltration (%)		51 (range 12–90)
Bone lesions		9/15 (60%)
Serum monoclonal protein		9/15 (60%): not detectable 6/15 (27%): <6% (2.4 g/L) 1/15 (6.5%): 13% (8.5 g/L) 1/15 (6.5%): 34% (33.9 g/L)
		Reference range
Median urine protein (g/24 h)		1.6 (range 0.4–8.2) <0.14
Urine immunofixation positive		11/15 (73%)
Median serum β2 microglobulin (mg/L)		6.0 (range 2.1–16.2) 0.8–2.2
Median serum albumin (g/L)		39.2 (range 28.6–50.6) 35.0–52.0
Median serum calcium (mg/dL)		9.1 (range 8.6–11.0) 8.5–10.3
Median hemoglobin (g/L)		115 (range 75–159) 120–160
Median WBC count (10^9/L)		7.0 (range 4.4–15.2) 4.0–11.0
Median platelet count (10^9/L)		207 (range 14–305) 140–440
Median serum lactate dehydrogenase (U/L)		250 (range 165–366) 135–225

A cytogenetic analysis via fluorescence in situ hybridization (FISH) was performed in nine of fifteen subjects and the results are shown in Table 2. The deletion of 13q was detected in all patients studied, followed by IGH gene rearrangements (14q32(IGH) and 4p16(FGFR3)), the deletion of 17p (17p13(p53)), and the amplification of 1q21 (3/9). Collectively, two patients were classified as Stage II and the other seven as Stage III. Interestingly, eight patients had a history of malignancies, such as bladder cancer (n = 3), colon cancer (n = 1), breast cancer (n = 2), lung cancer (n = 1), and skin cancer (n = 1), and three subjects were diagnosed as affected by amyloidosis.

Table 2. Genetic, treatment, and outcome data of patients with IgD myeloma.

		Number of subjects
Identified chromosomal abnormalities		
	Deletion of 13q14(DLEU)	9
	Translocation of 14q32(IGH)	5
	Translocation of 4p16(FGFR3)	4
	Deletion of 17p13(p53)	3
	Amplification of 1q21(CKS1B)	3
	Amplification of 11q13(CCND1)	2
	Deletion of 1p32(CDKN2C)	1
Treatment	Conventional chemotherapy	1
	Bortezomib–melphalan–prednisone (VMP)	4
	Bortezomib + dexamethasone (VD)	1
	Bortezomib-lenalidomide-dexamethasone (VRD)	1
	VD regimen + thalidomide (VTD)	1
	Lenalidomide + dexamethasone + ASCT	1
	Conventional chemotherapy + ASCT	4

Table 2. *Cont.*

Outcome	Transplant group:	
	VGPR	2
	CR	3
	Non-transplant group:	
	PR	4
	SD	4

See Materials and Methods for details: the non-transplant group received chemotherapy treatments; the transplant group received chemotherapeutic drugs followed by autologous stem cell transplantation. Abbreviations: ASCT: autologous stem cell transplantation; CR: complete response; VGPR: very good partial response; PR: partial response; SD: stable disease.

Considering therapy regimens, one patient was treated with conventional chemotherapy (CC), such as a vincristine–doxorubicin–dexamethasone (VAD) regimen; four with treatments with new agents, such as bortezomib–melphalan–prednisone (VMP), bortezomib plus dexamethasone (VD), lenalidomide plus dexamethasone (RD) followed by autologous stem cell transplantation (ASCT), bortezomib–lenalidomide–dexamethasone (VRD), and VD regimen plus thalidomide (VTD); four underwent CC followed by ASCT; and the last two cases died 4 and 10 months after the diagnosis of IgD MM, respectively (Table 2).

Ultimately, 11 of the 15 patients died (73.3%), and, taking into consideration that 11 patients presented severe pathologies at the moment of diagnosis of IgD MM and that 2 cases were identified in the last year and are currently alive, they are, therefore, not included in data analysis of OS; the overall median (interquartile range, IQR) OS was 24 months (12–144). Due to the low number of cases, we did not perform the Kaplan–Meier method to determine the survival differences between the transplant and non-transplant groups, but we analyzed the median OS values obtained. In the group of non-transplant subjects (n = 8) the median OS was 18 months (12–144), while in the group of transplant subjects (n = 5), the median OS was 48 months (36–120), and despite the low number of cases available, the difference in OS between the two groups was significant (p = 0.004). Evaluating the treatment responses, also using deceased subjects, a PR or SD was achieved in the non-transplant group, while in the transplant group, the patients obtained a VGPR or CR (Table 2). Moreover, considering the type of treatment, we observed an increased median OS from 12 months in the subject treated with conventional chemotherapy, to 30 months (12–84) in patients treated with new drugs, to 48 months (36–120) in individuals treated with conventional chemotherapeutic drugs followed by ASCT ($p < 0.05$). Finally, we investigated whether the detected chromosomal aberrations had an impact on OS and treatment response, but we did not observe any statistically significant differences ($p > 0.05$).

A regression model to determine prognostic factors was not performed, due to the low number of cases. However, we observed differences in the median values of four laboratory biochemical parameters between the group of subjects who died (n = 11) and those of patients who are currently alive (n = 4): (I) plasma cells in bone marrow, 70% (25–90) vs. 40% (35–80); (II) hemoglobin, 108 g/L (100–151) vs. 131 g/L (122–159); (III) β_2-microglobulin, 5.2 mg/L (3.9–16.2) vs. 3.1 mg/L (2.2–7.0); and (IV) albumin 39 g/L (34–44) vs. 43 g/L (37–51).

4. Discussion

IgD multiple myeloma accounts for about 1–2% of subjects affected by myeloma worldwide. Given the rarity of this myeloma subtype, knowledge is restricted to the few works published in the literature [2,3,5]. Here, we present the clinical and biochemical characteristics and outcomes of 15 patients admitted to the Fondazione IRCCS San Gerardo dei Tintori in 2008–2021 and diagnosed as suffering from IgD MM. In our hospital, the incidence of IgD MM was about 1%, in agreement with the worldwide incidence, but lower compared to 5.4% and 7.5% reported in two different Chinese centers, and to 2–8.8%

determined in a multicenter study from the Asian Myeloma network [2,3,6]. Although the Chinese population might be more affected by IgD MM than the Caucasian population, many hospitals in China do not assess the presence of IgD, thus determining a referral bias in incidence evaluation, as previously reported [2,3,6,7]. The clinical and biological characteristics of the patients enrolled in this study were similar to those identified in other works [3,6–8]. Male subjects were much more affected by this pathology than females. The λ light chains are found in 80% of patients and almost all had Bence–Jones proteinuria, as previously reported [2,3,5,6]. Subjects affected by IgD MM showed advanced age at the moment of diagnosis and more serious clinical features, particularly renal dysfunction, bone pains, and high degrees of bone marrow infiltration. Moreover, we observed that most of our patients had a clinical history of malignancies, which makes this pathology even more aggressive and with poor prognosis.

Several subjects affected by multiple myeloma show genetic aberrations, and cytogenetic analysis using FISH methodology is used to stratify patients with different genotypes. In our study, the deletion of 13q, IGH gene rearrangements (4p16(FGFR3) and 14q32(IGH)), the deletion of 17p (17p13(p53)), and the amplification of 1q21 (3/9)—which were associated with numerous cancers, such as chronic lymphocytic leukemia, multiple myeloma, and non-Hodgkin lymphoma—were detected [13]. We did not observe any association between the genetic alterations detected and survival time/poor prognosis. Reviewing the literature, different works analyzed these possible relationships in IgD MM patients. Wang and coauthors described that 1q21 amplification is associated with poor prognosis, while Chen and coauthors reported that the deletion of 13q, the amplification of 1q21, or translocation t(11;14) had no relationship with prognosis [2,3]. Recently, Liu and coworkers observed that the presence of 13q deletion, 1q21 amplification, and translocation t(11;14) was significantly different between IgD and non-IgD patients; particularly, t(11;14) was detected more frequently in IgD patients, although it is not considered a high-risk cytogenetic alteration in myeloma and, therefore, not related to a poor prognosis [6]. Moreover, Corre and coauthors clearly showed the extremely poor outcome of patients displaying the deletion of 17p (17p13(p53)), confirming its value as a prognostic indicator for poor outcomes [14]. In fact, our three patients presenting the "double hit" 17p (17p13(p53)) died within two years after the diagnosis of multiple myeloma. The molecular mechanisms in IgD myeloma remain unclear as of yet, and further research is needed. On the other hand, concerning biochemical parameters, LDH values were higher than the reference ranges in most of our patients, and high values have been associated with shorter overall survival [3].

Studies on IgD MM reported that subjects affected by IgD MM presented a shorter survival time than those affected by more common subtypes of myeloma [2–7,15–18]. Despite the low number of cases analyzed, our overall median OS of 24 months was inferior to those reported in the literature. This discrepancy could be explained by the introduction in the last decade of novel agents in the treatments, such as bortezomib (a proteasome inhibitor), thalidomide (an immunomodulatory agent), and lenalidomide (an immunomodulatory agent) other than conventional chemotherapy drugs, and, particularly, the autologous stem cell transplantation. These new options have improved the survival of IgD patients, resulting in prolonged times similar to those of subjects suffering from non-IgD myeloma [3,5,6]. In our study, most of our non-transplant subjects rapidly died and had advanced disease at the time of diagnosis. However, considering the patients treated with new chemotherapeutic drugs and those who received conventional chemotherapy drugs followed by ASCT, the median OS increased to 48 months, a result that is double compared to our overall average and more in agreement with the literature data [7,8,19,20]. However, the matter remains open to debate, and further research is needed to unravel biological mechanisms that link treatments to survival.

Our study presents some limitations that should be considered. The work was retrospective and performed in a single center, and the small sample size, missing data, and heterogeneous treatments limited the statistical analysis. A larger number of individuals

is needed in order to improve the accuracy of our results and the knowledge of this rare subtype of myeloma.

5. Conclusions

Collectively, our study suggests that IgD myeloma is rare but most probably an underestimated pathology and that the laboratory has a fundamental role in early detection, and it should be mandatory to assess the presence of IgD proteins when free light chains and no heavy chain counterpart are identified via immunofixation, as also recently highlighted by Egan and coauthors [7]. In fact, there are still many laboratories that do not detect IgD monoclonal protein since it is too rare, as recently reported not only for IgD MM but also for IgE MM [21,22]. Therefore, it is important to continuously study and monitor IgD MM cases at local and national levels in order to increase the knowledge and the detection of this disease, to facilitate the development of risk-stratification treatments, and to enhance patient prognoses.

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