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Original Article

Cytogenetic, Clinical, Hematologic, Demographic, Immunohistochemical, and Flow Cytometry Characteristics of Patients with Plasma Cell Neoplasm in Five Years: A First Report from Iran

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Abstract

Background: The aggregation of clonal plasma cells causes plasma cell neoplasms, which vary in severity and clinical outcomes. The present research focused on the epidemiological, clinical, immunologic, and cytogenetic characteristics of plasma cell neoplasms.

Methods: In this five-year retrospective cross-sectional study, demographic information such as age and sex, calcium elevation, renal insufficiency, anemia, and bone lesion (CRAB) characteristics, as well as laboratory data including bone marrow and peripheral blood film results, immunohistochemistry, flow cytometry, and cytogenetic study outcomes were collected at Shiraz University of Medical Sciences, Shiraz, Iran. The collected data were analyzed using SPSS Statistics software (version 20.0). Descriptive statistics were reported as numbers, percentages, and mean±SD.

Results: 417 newly diagnosed plasma cell neoplasm patients were confirmed by bone marrow or other tissue biopsy tests. 279 patients were men (66.9%). The most prevalent age group was 60-64 years old (18.46%). Plasma cell myeloma (PCM) affected 355 (85.13%) patients, while monoclonal gammopathy of undetermined significance (MGUS) affected 6 (1.43%) patients. Solitary plasmacytoma was seen in 56 (13.42%) patients. At the time of diagnosis, 119 (33.52%) of 355 PCM patients were asymptomatic, whereas 236 (66.47%) patients had at least one CRAB symptom, 55 (15.49%) had two or more, and 14 (3.94%) had three or more. There were 7 (1.97%) cases of amyloidosis. Cytogenetic abnormalities were found in 51.28% (40/78) of the patients. Twenty-one individuals (52.5%) were hyperdiploid with multiple trisomy, while 19 (47.50%) were not.

Conclusion: When diagnosed, Iranian PCM patients might have more advanced disease. PCM was more prevalent in young adults, and hyperdiploid was the most common cytogenetic finding in this investigation.

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Keywords ● Plasmacytoma ● Multiple myeloma ● Cytogenetics

What's Known

- Plasma cell myeloma (PCM) is rare in young adults.
- 30-40% of newly diagnosed myeloma patients exhibited numerical or structural cytogenetic abnormalities.
- Abnormalities related to hyperdiploid typically involve odd-numbered chromosomes (trisomies) of 3, 5, 7, 9, 11, 15, 19, and 21.

What's New

- A higher prevalence of PCM in young adults was observed, either as a result of the larger sample size of the present study or as a result of variations in quality of life, health services, and medical scientific research between developed and developing countries.
- In this study, the karyotype of 48.72% of PCM patients was normal.
- In the present study, the hyperdiploid group (47.50%) had the highest frequency of chromosome 19 trisomy.

Introduction

Plasma cell neoplasms cause end-organ damage by accumulating clonal plasma cells and overproducing monoclonal proteins.

Plasma cell neoplasms compose of multiple myeloma (MM)/plasma cell myeloma (PCM) and its asymptomatic precursors, non-IgM monoclonal gammopathy of unknown significance (MGUS), and smoldering multiple myeloma (SMM), as well as localized illnesses such as solitary plasmacytoma (SP) and POEMS syndrome.[1] From 1990 to 2016, PCM incidence increased to 126%, and the death toll increased to 94%.[2] It's more common in industrialized countries.[3] It is the second most frequent type of blood cancer.[4] PCM increases with age. The prognosis for PCM patients has improved, and their five-year survival rate (SR) is 50%.[4] Age-standardized 10-year and 20-year PCM SR improved from 18.1% and 8%, in 2002-2006, to 34.9% and 19.9%, respectively, in 2012-2016.[5] Multiple myeloma has become more common in several countries due to aging populations and enhanced survival.

Almost all cases of multiple myeloma are caused by premalignant asymptomatic monoclonal gammopathy (MGUS). MGUS affects 3% of people over the age of 50 and 5% of people over the age of 70.[6] Based on its subtypes, MGUS has a 0.3% to 1.5% annual probability of developing PCM.[7] MGUS is characterized by a serum non-IgM-type monoclonal protein concentration of <3 g/dL, less than 10% clonal BM plasma cells, and no end-organ damage.[8, 9]

Active PCM requires end-organ damage (CRAB features: hypercalcemia, renal failure, anemia, lytic bone lesions) or 60% clonal plasma cells in BM or involved to uninvolved serum free light-chain (sFLC) ratio>100 or focal lesion >1 on MRI. All PCMs require more than 10% clonal plasma cells in bone marrow (BM) and/or a biopsy-confirmed bony or extramedullary plasmacytoma. CRAB describes numerous myeloma symptoms (C-Calcium elevation [>11 mg/dL]/R-Renal dysfunction [Serum creatinine>2 mg/dL]/A-Anemia [hemoglobin<10 g/dL or >2 g/dL drop from normal patient]/B-Bone disease [one osteolytic lesion on skeletal radiography]). All CRAB characteristics must be caused by the plasma cell disease. Patients with multiple myeloma have non-CRAB clinical symptoms such as neuropathy, extramedullary disease, hyperviscosity syndrome, and amyloidosis.

PCM primary and secondary cytogenetic abnormalities are distinguished by metaphase karyotyping or fluorescent *in situ* hybridization (FISH). Primary cytogenetic abnormalities are supposed to occur during MGUS and may have an impact on MGUS pathogenesis. Secondary cytogenetic abnormalities can affect the course of any subtype of PCM. In the present study, we assessed the epidemiological, clinical, cytogenetic, and laboratory characteristics of patients with plasma cell neoplasms, predominantly PCM, at a single-center surgical pathology laboratory in Iran from March 2016 to March 2021. Recognizing these characteristics might help in diagnosis and treatment.

Materials and Methods

In this retrospective cross-sectional study, the pathology laboratory data including Immunohistochemistry (IHC), molecular, and cytogenetics were reviewed for patients with plasma cell neoplasms from March 2016 to March 2021. This study was conducted in the Subdivision of Hematopathology, Department of Pathology, Shiraz University of Medical Sciences (Shiraz, Iran). The data was extracted from systemic data. This study was approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.MED.REC.1401.012).

Demographic information including age, sex, CRAB features, serum monoclonal protein greater than 3 g/dL, and laboratory data were extracted from patients' medical records. BM aspiration was processed for smears, flow cytometry, molecular diagnostics, and cytogenetics. Immunohistochemistry (IHC) staining was performed on paraffin slices of BM trephine core biopsies. IHC was performed using CD138, kappa, and lambda monoclonal antibodies. Flow cytometric antibodies for CD38, CD138, CD56, and CD19 were evaluated. Before the cytogenetic investigation, bone marrow was cultured in unstimulated medium for 72 hours. Metaphase spreads were G-banded. At least 15 metaphases were examined in each case. Aberrations were classified using the 2016 ISCN nomenclature.

All cases were diagnosed using updated International Myeloma Working Group (IMWG) criteria for multiple myeloma and related plasma cell diseases.[8] Patients without plasma cell neoplasms were excluded.

Statistical Analysis

Data were analyzed using SPSS software, version 20.0 (IBM, USA). The results were expressed as number, percentage, mean±SD, and minimum-maximum, where required.

Results

This retrospective cross-sectional study included 417 newly diagnosed plasma cell neoplasm patients, whose diagnoses were confirmed by bone marrow or other tissue biopsy examinations. The male group had 279

(66.91%) patients, and the female group had 138 (33.09%) patients. Patients were grouped by age in five-year intervals. The most common age group was 60-64 years old (18.46%).

Individuals were divided into three groups based on the IMWG diagnostic criteria: PCM, MGUS, and SP. PCM had 355 (85.13%) patients, while MGUS had 6 (1.43%) patients. Besides, plasmacytoma was found in 56 (13.42%) patients.

PCM Statistical Analysis

Table 1 summarizes PCM patients' demographics, clinical characteristics, presenting symptoms, and laboratory results. By the end of the research, 75 patients (21.12%) had relapsed or progressed from PCM. Plasma cell leukemia (PCL) can emerge without a prior history of multiple myeloma (primary PCL [PPCL]) or as a leukemic shift in advanced, relapsed, or treatment-resistant PCM (secondary

Table 1: Baseline demographics and clinical characteristics of plasma cell myeloma patients

Variable		Frequency n (%) (N=355)
Sex (%)	Male	237 (66.76)
	Female	118 (33.24)
Age, (mean±SD, range)		62.15±11.77 (29-94)
Hb, g/dL, (mean±SD, range)		9.60±2.27 (3.90-15.80)
WBC ($\times 10^9$/L), (mean±SD, range)		6.66±6.15 (1-84)
PLT ($\times 10^9$/L), (mean±SD, range)		167±100 (10-720)
Creatinine, mg/dL, (mean±SD, range)		2.96±0.52 (0.70-18.10)
Ca, mg/dL, (mean±SD, range)		9.48±1.54 (6.40-14.30)
BMAPCs, %, (mean±SD, range)		34.42±25.62 (1-95)
BMBPCs, %, (mean±SD, range)		66.66±34.06 (10-95)
CRAB features	0	119 (33.53)
	≥1	236 (66.47)
	≥2	55 (15.49)
	≥3	14 (3.94)
Anaemia (Hb<10 g/dL)		228 (64.22)
Renal insufficiency (Cr>2 mg/dL)		46 (12.95)
Hypercalcemia (Ca>11 mg/dL)		11 (3.09)
Bone lesions		19 (5.35)
Amyloidosis		7 (1.97)
PCs (peripheral blood), %, Mean (range)		18.01 (1-65)
PCs (peripheral blood) ≥20% at presentation (PCLs)		14 (3.94)
PCs (peripheral blood) in PCLs, %, Mean (range)		41.86 (24-65)
PPCL		10 (71.42)
SPCL		4 (28.57)
Plasmacytoma at presentation		40 (11.26)
Site of plasmacytoma (n=40)	Bone (SBP)	35 (87.50)
	Extramedullary (EMP)	5 (12.50)
SBP location	Vertebrae (T-spine, L-spine, Sacrum)	17 (42.50)
	Chest wall (Sternum, Ribs, Clavicle)	14 (35)
	Pelvis (iliac)	2 (5)
	Extremities (femur, humerus)	2 (5)
EMP location	Retroperitoneom	2 (5)
	Cerebrum	1 (2.50)
	Parotid	1 (2.50)
	Stomach	1 (2.50)
Light chain type, n (%):	κ	154 (53.84)
	λ	127 (44.40)
PCs in MFC, %, Mean (range)		16.54±17.98(0.50-83)
Expression of markers (CD19)	Positive	33 (17.78)
	Negative	153 (82.22)
Expression of markers (CD56)	Positive	149 (86.13)
	Negative	24 (13.87)
Cytogenetics, (n=78), n (%)	Abnormal karyotype	40 (51.28)
	Normal karyotype	38 (48.72)

BMAPCs: Bone marrow aspiration plasma cells; BMBPCs: Bone marrow biopsy plasma cells; PPCL: Primary plasma cell leukemia; SPCL: Secondary plasma cell leukemia; MFC: Multicolor flow cytometry

Table 2: Primary and secondary cytogenetic abnormalities in plasma cell myeloma patients

Abnormality			Overall (n=40) number (%) of patients	Gene(s)/ chromosomes affected	Cytogenetic risk stratification	Prognostic clinical impact
Primary events	Hyperdiploidy		21 (52.50)		Standard risk	Favorable
	Trisomy (ies) without IgH abnormality		28 (70)	Odd numbered chr.	Standard risk	Favorable
	Trisomy 19		19 (47.50)		Standard risk	Favorable
	Trisomy 15		16 (40)		Standard risk	Favorable
	Trisomy 11		16 (40)		Standard risk	Favorable
	Trisomy 21		13 (32.50)		Standard risk	Favorable
	Trisomy 9		12 (30)		Standard risk	Favorable
	Trisomy 3		12 (30)		Standard risk	Favorable
	Trisomy 5		11 (27.50)		Standard risk	Favorable
	Trisomy 7		10 (25)		Standard risk	Favorable
	Trisomy 1		6 (15)		Standard risk	Favorable
	Non-Hyperdiploidy		19 (47.50)		High risk	Adverse
	IgH translocations (14q32 rearrangements)		5 (12.50)			
	t (11;14)		1 (2.50)	CCND1	Standard risk	Neutral
	t (14;16)		2 (5)	C-MAF/MAF	High risk	Adverse
	Combined IgH translocation/ trisomy		3 (7.50)			
	Combined high-risk IgH translocation/trisomy		1 (2.50)		High risk	
	Isolated monosomy 14		4 (10)			Unknown
	Polyploidy		3 (7.50)			Favorable
	Triploidy		1 (2.50)			Favorable
	Tetraploidy		2 (5)			Favorable
Other cytogenetic abnormalities	t (3;7)		1 (2.50)			
	t (6;11)		1 (2.50)			
	t (6;9)		1 (2.50)			
	t (7;9)		1(2.50)			
	t (16;17)		1 (2.50)			
	t (17;18)		1 (2.50)			
	t (12;19)		1 (2.50)			
	t (1;14)		1 (2.50)			
Secondary events	Gains	1q	13 (32.50)	CKS1B and ANP32E	High risk	Adverse
		6p	8 (20)			
		12p	2 (5)	LTBR		
		17q	5 (12.50)	NIK		
	Deletions	1p	9 (22.50)	CDKN2C and FAM46C	High risk	Adverse
		6q	11 (27.50)			
		8p	5 (12.50)			
		11q	3 (7.50)	BIRC2 and BIRC3		
		13q/ monosomy 13	14 (35)	RB1 and DIS3 and EBPL	Standard risk	Adverse
		14q	4 (10)	TRAF3		
		16q	3 (7.50)	CYLD and WWOX		
		17p	4 (10)	TP53	High risk	Adverse
	Translocations	t (8;14)	1 (2.50)	MYC	Controversial	
No high-risk cytogenetic abnormality			20 (50)			
One high-risk cytogenetic abnormality			20 (50)		High risk	Adverse
Double-hit (two high-risk cytogenetic abnormality)			8 (20)		High risk	Adverse
Triple-hit (three high-risk cytogenetic abnormality)			1 (2.50)		High risk	Adverse

PCL [SPCL]). Ten patients were diagnosed with PPCL and four with SPCL.

Multiple myeloma was presented as a bone (solitary bone plasmacytoma [SBP]) or extramedullary plasmacytoma (EMP) in 40 cases of 355 PCM patients. Plasmacytomas were found in 87.50% of patients (35/40) as SBPs, and 12.50% were EMPs. The majority of malignancies (42.50%) were found in the spine.

111 patients (31.26%) had rouleaux formation, 57 (16.05%) had left shift, 18 (5.07%) had nucleated red blood cells (NRBC), 13 (3.66%) had leucoerythroblastic reactions, and 37 (10.42%) had circulating plasma cells (CPCs), of which 14 (3.94%) had plasma cell leukemia. There was leukopenia in 86 (24.22%) patients, thrombocytopenia in 129 (36.33%), and pancytopenia in 65 (18.30%) patients. Leukocytosis affected 40 patients (11.26%), and thrombocytosis affected 2 (0.56%). The majority of the patients had normocytic (90.59%) or normochromic anemia (80.91%), while others had hypochromic (19.08%), microcytic (4.84%), macrocytic (2.27%), or hyperchromic (0.56%) anemia.

Non-secretor variant PCM was found in two PCM individuals who lacked kappa or lambda light chain restriction. One patient with plasma cell myeloma had biphenotypic PCM with dual kappa and lambda light chain expression. The genetic alterations found in plasma cell myeloma patients are shown in table 2.

Solitary Plasmacytoma Statistical Analysis

Between 2016 and 2021, Faghihi Teaching Hospital database recorded 56 cases of SP. The male-to-female ratio was 2.29:1.

Tables 3 and 4 summarize the clinical and laboratory data of SP patients. At the time of diagnosis, the nine EMP patients had a mean age of 51.22±19.45 (range 6-80). All of the EMP patients were men. The median age of 47 SBP patients was 56.89 (range: 8-88), and the male-to-female ratio was 1.76:1. Each patient had an IMWG-recommended histologic diagnosis of SBP or EMP.[9] At the time of diagnosis, 26 of the 56 cases had BM testing, and less than 10% of SP patients had BM involvement.

The CBC and PBS data were available for

Table 3: Baseline demographics and clinical characteristics of solitary plasmacytoma patients

Variables		Number (N=56)
Sex (%)	Male	39 (69.65)
	Female	17 (30.35)
Age, (mean±SD, range)		55.98±18.43 (6-88)
Hb, g/dL, (mean±SD, range)		13.45±1.47 (10.60-15.60)
WBC (×10^9/L), (mean±SD, range)		5.93±2.60 (2.10-13.60)
PLT (×10^9/L), (mean±SD, range)		247±138 (82-659)
BMAPCs, %, (mean±SD, range)		2.65±1.57 (1-6)
BMBPCs, %, (mean±SD, range)		4.57±3.21 (1-10)
PCs in MFC of Bone Marrow aspiration, %, (mean±SD, range)		1.24±1.78(0.50-7.50)
Site of plasmacytoma	Bone (SBP)	46 (82.14)
	Extramedullary (EMP)	9 (16.07)
	Multiple solitary plasmacytoma (MSP)	1 (1.78)

Table 4: Anatomic Location of solitary plasmacytoma

SP location	N (%)
Solitary plasmacytoma of bone	N=46
Vertebrae (T-spine, L-spine, Sacrum)	26 (46.42)
Chest wall (Sternum, Ribs, Clavicle)	13 (23.21)
Pelvis (Iliac)	4 (7.14)
Shoulder	2 (3.57)
Extremities (Femur)	1 (1.78)
Solitary Extramedullary plasmacytoma	N=10
Retroperitoneal mass	2 (3.57)
Spinal extradural mass	2 (3.57)
Nasopharynx	1 (1.78)
Lymph Node (Inguinal)	1 (1.78)
Lung	1 (1.78)
Abdominal wall (Soft tissue)	1 (1.78)
Pelvic mass	1 (1.78)
Both vertebral and chest wall plasmacytoma	1 (1.78)

Table 5: Baseline demographic and clinical characteristics of Monoclonal Gammopathy of Undetermined Significance patients

Variables		Number (N=6)
Sex (%)	Male	3 (50)
	Female	3 (50)
Age, (mean±SD, range)		49.50±11.47 (40-66)
Hb, g/dL, (mean±SD, range)		13.30±1.50 (11.10-14.70)
WBC (×10^9/L), (mean±SD, range)		6.10±4 (2.30-12.90)
PLT (×10^9/L), (mean±SD, range)		169±55 (121-242)
BMAPCs, %, (mean±SD, range)		4.83±2.99 (1-9)
BMBPCs, %, (mean±SD, range)		5.75±2.66 (2.50-9)
Light chain type, n (%)	κ	4 (66.66)
	λ	2 (33.33)
PCs in MFC, %, (mean±SD, range)		0.67±0.23 (0.50-1)

BMAPCs: Bone marrow aspiration plasma cells; BMBPCs: Bone marrow biopsy plasma cells; MFC: Multicolor flow cytometry; PC: Plasma Cell

26 of the 56 SP patients. There were no cases of CPC, NRBC, leucoerythroblastic response, rouleax, or leukocytosis. One patient (3.84%) had a left shift of white blood cells. Five patients (19.23%) had anemia, 4 (15.38%) had leukopenia, 2 (7.69%) had thrombocytopenia, and 1 (3.84%) had pancytopenia. There were two cases of thrombocytosis (7.69%). Three patients (11.53%) had hypercellular marrow, 17 (65.38%) had normocellular marrow, and 6 (23.17%) had hypocellular marrow. Only one SP patient received a cytogenetic analysis, which revealed no abnormalities.

MGUS Statistical Analysis

Between 2016 and 2021, the database of Faghihi Hospital showed six cases of MGUS. The sex ratio was 1:1 (M: F). The clinical and laboratory characteristics of MGUS patients are summarized in table 5. According to CBC and peripheral blood smear (PBS) findings, all patients had normal RBC shape and were free of anemia. As indicated in table 5, 16.66% of patients had leukopenia, 33.3% had thrombocytopenia, and none had pancytopenia. Leukocytosis occurred in 2 (33.33%) of the patients.

Five patients (83.33%) had normocellular bone marrow, while one patient (16.66%) had hypocellular marrow. In a polyclonal background, all immunohistochemically labeled tissues had clonal plasma cells (less than 10%). Flow cytometry was performed on four MGUS patients, and half of them had a small population of abnormal plasma cells with $CD19^-$ or $CD56^+$. None of the MGUS were cytogenetically analyzed.

Discussion

In this study, we investigated a hospital database for patients who were diagnosed with plasma cell neoplasm. Over a five-year period, 417 patients with the aforementioned diagnosis were found. PCM was found in 355 of them. Cytogenetic studies were performed on 78 PCM patients, of which 40 patients had karyotype abnormalities.

The age range of PCM patients was from 29 to 94 years, with a median age of 62.15 years; 36% were 60 to 70 years old, with a male preponderance. The findings were consistent with those of Tang and colleagues[10] and Jalaeikhoo and colleagues,[11] who found that patients were 67.6, and 61.9 years old, respectively. Males outnumbered females in a 2:1 ratio. Our patients were predominantly over the age of 40 (96%).

14 (3.94%) of 355 plasma cell myeloma patients were young adults (25–39 years). Since PCM is uncommon in this age range, few studies have focused on young adults. The present cross-sectional study had more young adults with PCM than Nakaya and others in Japan (0.8%).[12] The higher prevalence of PCM in young adults, which was seen in this study, could be attributed to a smaller study group diagnosed with PCM or to variations in the quality of life, health services, and medical scientific research between developed and developing countries.

The CRAB features of PCM were identified in this study. Anemia was usually caused by CRAB (64.22%). This was slightly higher than what previously was reported in other Iranian studies.[11, 13, 14] Anemia was observed in 57% of individuals with CRAB-positive symptomatic myeloma.[13] 28.16% had severe anemia (Hb8 g/dL).[14] Due to the small number of cases in these investigations, the findings might be influenced by fast-developing cases. There may be genetic and societal variances. Hypercalcemia and renal insufficiency were found in 3.9% and 12.9% of patients, respectively. The present study indicated that 12.95% of patients had blood creatinine levels of 2 mg/dL or above, which was lower than previous studies (22.1% to 86.4%).[11, 13] In addition, the prevalence of hypercalcemia

(Ca>11 mg/dL) and renal insufficiency (Cr>2 mg/dL) in PCM patients ranged from 6% to 47.5% and from 19% to 86.4%, respectively.[11, 13] This was most likely because most of our patients were transferred to this hospital in early stages of their illness, or due to hospital records were incomplete. Amyloidosis was found in seven patients (1.97%). Ajise and others identified a 3% amyloidosis incidence.[15]

At the time of diagnosis, 119 (33.52%) of these patients were asymptomatic, while 66.47% (n=236) had at least one CRAB symptom, and 69 (19.43%) had two or more. Few studies examined CRAB features in PCM patients simultaneously. According to Howell and colleagues, 29.9% of PCM patients were asymptomatic, 36.5% had one CRAB feature, and 32.8% had two or more.[16]

The prognosis for multiple myeloma with pancytopenia is poor.[4] In such cases, pancytopenia might be deceiving, delaying diagnosis and treatment.[11] In our study, 18.30% of PCM patients were pancytopenic. According to Jalaeikhoo and others, pancytopenia was seen in 8.9% of PCM patients.[11]

Among PCM patients for whom IHC analysis was performed, 154 (53.84%) were kappa restricted, and 127 (44.40%) were lambda restricted. Besides, 2 (0.69%) had neither kappa nor lambda light chain restriction and were diagnosed with non-secretory variant PCM, and 1 (0.35%) had coexpressed kappa and lambda light chains together and was diagnosed with biphenotypic variant PCM.

Multicolor flow cytometry (MFC) can detect abnormal marker expression, prognostic indications, and plasma cell monoclonal origins. CD56, also known as neural cell adhesion molecule (NCAM), is expressed in 70% of myelomas and could be used to differentiate between malignant and benign plasma cells, as well as MGUS, and plasmacytoid lymphomas, which have high levels of CD138 but no CD56.[17] CD56 expression was abnormal in 70-80% of flow cytometry analyses.[18] CD56 expression was correlated with increased lytic bone lesions but not with renal failure, hypercalcemia, or anemia.[19] Flow cytometry immunophenotyping was performed on 232 of 355 PCM patients. Based on CD19 and CD56 expression, 82.2% of these individuals had no CD19 expression, and 86.1% had CD56 aberrancy.

There was a significant difference in bone marrow plasma cell percentages when the different methods of observation were used.[20] When compared to data obtained by flow cytometry analysis of bone marrow aspiration with mean values of 16.54% (range 0.4%-83%), CD138 IHC staining of the core biopsy yielded the highest estimations of the plasma cell proportion with a mean of 66.66±34.06 (range 10%-95%). However, it was shown that PCM patients with MFC-based total PC>15% demonstrated poorer outcomes in BM immunophenotyping than PCM patients with total PC less than 15%.

Diagnostic bone marrow sampling and analysis are difficult to apply due to the low proliferative activity of malignant plasma cells and the small number of plasma cells in a haemodiluted bone marrow aspirate.[21] About 30-40% of newly diagnosed myeloma patients had cytogenetic abnormalities, either numerical or structural. Translocations and copy number aberrations were examples of structural aberrations (deletions or gains).[21] Hyperdiploid patients had 48-74 chromosomes; non-hyperdiploid patients had hypodiploidy, pseudodiploid, or near tetraploidy. Non-hyperdiploidy is connected to IgH translocations and has a bad prognosis.[22] From 78 participants of the present study who received cytogenetic testing, 38 (48.72%) had a normal karyotype and were diploid, while 40 (51.28%) had an abnormal karyotype. Genetic abnormalities were found in 22.1-75% of cases.[23, 24] 2.50% of these 40 individuals had hyperdiploidy with trisomies, while 19 (47.50%) did not.

Primary cytogenetic events, such as hyperdiploid and non-hyperdiploid abnormalities, and secondary cytogenetic events, especially MYC oncogene dysregulation, 1p, 17p, chromosome 13 loss, and 1q gain, contribute to PCM pathogenesis.[17] Odd-numbered chromosomes (trisomies) of 3, 5, 7, 9, 11, 15, 19, and 21 are typically involved in hyperdiploid disorders. In the present study, in the hyperdiploid group, trisomy of chromosome 19 was the most common and found in 19 individuals (47.50%), followed by chromosomes 15 (40%), 11 (40%), 21 (32.50%), 9 (30%), 3 (30%), 5 (27.50%), 7 (25%), and 1 (20%).

Five patients (12.50%) had 14q32 IgH translocations. This G-banding-based investigation found no translocations other than t (11; 14), t (14; 16), t (8; 14), and t (1;14). To increase the detection rate of genetic abnormalities in plasma cell myeloma cytogenetic analysis, FISH or microarray-based methods must be utilized in addition to traditional G-banding.

According to a study by Saxe and colleagues, 5% of myeloma patients had hyperdiploidic and IGH translocation.[25] Three aberrant karyotypes (or 7.5% of the total) in this study had hyperdiploidic and IGH translocations.

In our patients, four people (10%) had isolated monosomy 14. However, Hamdaoui and

colleagues achieved 4%.[23] The most common monosomies in the present study were 13, 20, 14, 22, 16, and 8, respectively.

At least one of the following poor-prognosis mutations is present in high-risk multiple myeloma: t (14;14), t (14;16), t (14;20), del 17p, p53 mutation, gain 1q, and del 1p.[22, 26] PCM with a "Double hit" has two high-risk genetic anomalies, while PCM with a "triple hit" has three. Double or triple-hit PCM might have worse consequences than PCM. Investigations on these topics are scarce so far. In 159 newly diagnosed PCM patients, Baysal and others reported seven double-hit and two triple-hit cases.[27] In the present study, 20 (50%) of the patients had one high-risk factor, 8 (20%) had two, and 1 (2.50%) had three.

The most common structural chromosomal alterations in PCM are chromosome 1 aberrations including mostly 1p deletions and 1q amplifications. Isochromosome 1q translocations and "whole arm" or "jumping" 1q translocations are particularly complex. In jumping 1q rearrangements, the complete arm of 1q is the donor chromosome, while any other chromosome might be the recipient. Unbalanced whole-arm (jumping) per centric 1q translocations were found in multiple myeloma patients.[25] Two patients (5%) in this study had jumping translocation 1q, and 1 (2%) had isochromosome 1q.

An SP involves a solitary mass of monoclonal plasma cells in the bones or extramedullary tissues. According to research, it accounted for 5-10% of all plasma cell neoplasms.[28] The ratio of SP to total plasma cell tumors was higher in the current study (13.42%) than in previous studies because the current study was conducted at one of the referral cancer centers in Iran, where many patients with solitary tumors come for diagnostic workups, whereas patients with anemia typically go to general centers.

In this study, we analyzed data from 56 individuals: 46 with bone SP (SBP), nine with extramedullary SP (EMP), and one with multiple bone SP (MSP). The median age at diagnosis was in the fifth decade of life, roughly eight years younger than the median age of MM diagnosis. The youngest patient with SBP in the vertebrae was eight years old, which indicated that the disease can strike at any age. The analysis of the literature confirmed our study's median age at diagnosis of 50-60 years and male preponderance.[29, 30] Ghiassi-Nejad and others conducted the largest epidemiologic retrospective analysis in the United States, evaluating patients from The National Cancer Database for Plasmacytoma between 2004 and 2013.[31] They reported that the studied patients were old and male predominated. As indicated in table 4, plasmacytoma in the vertebrae was found in 26/46 patients (56.52%), and SEP was more prevalent in the retroperitoneal/spinal extradural region (2/9 patients, 22.22%). The most common SBP locations in the current study were much the same as in previous investigations. Our analysis found different EMP locations than previous studies. This could be due to the our small sample size or upper respiratory SP patients being transferred to other tertiary hospitals for head and neck surgical cancer treatments. MSP was not commonly found in the literature. Basavaiah and others reported a case with MSP involving the L3 vertebra, right 10th rib, right scapula, bilateral shoulder, and posterior skull.[29]

MGUS has the potential to develop into a malignant plasma cell neoplasm. In this study, we focused on patients with less than 10% monoclonal plasma cells, no CRAB features, and less than 3 g/dL of monoclonal protein. By analyzing the surgical pathology database, six individuals (1.43%) with MGUS were found. In a similar study, Ajise and others found MGUS in 2% of 100 consecutive patient samples evaluated for plasma cell neoplasms. In 2010, the IMWG standards set a 10% diagnostic criterion for multiple myeloma.[15] This limit prevented the misclassification of MGUS patients as PCM. 10% plasma cells was not a clear criterion for PCM.[8] According to Jalaeikhoo and others, 20% of individuals with 5-10% plasma cells in bone marrow biopsies might have PCM, especially when initial evaluations indicated an apparent M-spike in electrophoresis or the presence of two CRAB characteristics simultaneously.[32] Therefore, these patients should be investigated further.

Monoclonal gammopathy of renal significance (MGRS) has become more common in recent years.[33-36] MGRS is defined as any B cell or plasma cell clonal lymph proliferation with both of the following features: (1) one or more kidney lesions associated with the production of monoclonal immunoglobulin production; (2) an underlying B cell or plasma cell clone with no cancer consequences and no hematological criteria for specialized therapy.[37] Renal amyloidosis, light chain deposition disease, glomerulopathies, and nephrotic syndrome are all MGRS-related renal lesions.[36] This study found a patient with MGUS-associated nephropathy (MGRS). A 49-year-old female MGUS patient with renal AL amyloidosis (amyloid proteins were also identified on renal biopsy) and high blood creatinine met MGRS diagnostic criteria.

Some of the limitations of the present study

were all of the laboratory results of the patients were not complete in the system database, and also the lack of access to patients to attain the patient's survival. Therefore, it is recommended that future studies compare the patient's survival with their laboratory and cytogenetic findings.

Conclusion

Iranian PCM patients might have been diagnosed with more advanced diseases based on their CRAB indications and laboratory findings. PCM had greater prevalence in young individuals, and hyperdiploid was the most common cytogenetic finding in this study.

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Authors' Contribution

M.Sh: Study design, data analysis, drafting; SE.H: Data gathering, data analysis, drafting; N.O: Study concept, data analysis, drafting and preparing the tables; M.M: Data analysis, drafting and preparing the tables; A.S: Data analysis and interpretation, drafting; All authors read and approved the final manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

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