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ORIGINAL ARTICLE

Distinct Clinical Features of Plasma Cell Myeloma Patients Exhibiting Dysmorphic Plasma Cells: Association with More Plasma Cells at Diagnosis

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Abstract Dysmorphic plasma cells are occasionally found in bone marrow (BM) aspirates of plasma cell myeloma (PCM) patients. We retrospectively analyzed the incidences of significant dysmorphic plasma cells (SDPC) presentations and their associations with clinical features in PCM patients. Total 91 PCM patients diagnosed from January 2013 to December 2017 at author's institution were enrolled. SDPC presentation was determined as $\geq$ 5% (SDPC5) or $\geq$ 10% (SDPC10) among total PC and clinical features of PCM patients were compared with respect to SDPC presentation status. Incidence of SDPC5/SDPC10 presentation was 39.6%/18.7%. Patients with SDPC5/SDPC10 showed significantly more BM PC (P = 0.004/0.020) and higher incidences of *CKS1B* gains (P = 0.022/0.001) and *RB1* loss (P = 0.032 for SDPC10 only) at diagnosis than those without SDPC5/SDPC10. Patients with SDPC5/SDPC10 also showed significantly greater absolute BM PC (P = 0.007/0.034 and 0.047/0.049 for 1st and 2nd follow-up, respectively) and serum M-protein (P = 0.041/0.044 and 0.039/0.049 for 1st and 2nd follow-up, respectively) reductions after chemotherapy than those without SDPC5/SDPC10. SDPC5/SDPC10 presentation was confirmed as an independent predictor of BM PC $\geq$ 37.7% [hazard ratio (HR) 4.649/2.613, P = 0.005/0.039]. Our present study demonstrated that SDPC presentation would be an independent predictor of more BM PC at diagnosis in PCM patients. Associations between SDPC presentation and higher incidence of *CKS1B* gains and *RB1* loss, greater PC/serum monoclonal protein reductions after chemotherapy were also identified. Association between SDPC presentation and favorable treatment response should be evaluated in more comprehensive study.

Keywords Clinical features · Dysmorphic plasma cells · Plasma cell myeloma

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Introduction

Poor prognostic markers for plasma cell myeloma (PCM) included in the international staging system (ISS) for PCM are high serum beta-2-microglobulin level (β2M) and low serum albumin level [1, 2]. Recently revised ISS (R-ISS) for PCM included serum lactate dehydrogenase (LDH) levels, fluorescence in situ hybridization (FISH) results such as *TP53* loss indicating del(17p), *FGFR3-IGH* and *IGH-MAF* rearrangement indicating t(4;14) and t(14;16) translocations, respectively as prognostic markers [2]. Other prognostic factors in MM include presence of plasmablasts in bone marrow (BM) aspirates, presence of genetic abnormalities such as t(11;14) for good prognosis and 1q gains indicating *CKS1B* gains for poor prognosis in karyotype and/or FISH analyses, and/or 13q deletion indicating *RB1* loss for poor prognosis [1, 3–5].

Dysplasia in > 10% of trilineage hematopoietic cells has been defined as significant dysplasia for the diagnosis of

myelodysplastic syndrome (MDS) [6, 7] but associations between dysplastic features of other neoplastic cells and clinical importance of them was not addressed. In the PCM, the majority of neoplastic PC show typical morphology such as single, round, eccentric nucleus and perinuclear halo in the cytoplasm. However, a recent case study reported the presence of multinucleated "dysmorphic" PC which shows abnormal morphology from classical PC, in the PB of the plasma cell leukemia patient [8] and in some cases of PCM, neoplastic PC with similar dysmorphic features such as binucleation, multinucleation, prominent nucleoli and irregular shape in the cytoplasm can be also observed. In the present study, we retrospectively analyzed the incidences of dysmorphic PC presentations in the PCM and their associations with clinical features of PCM patients.

Materials and Methods

Patient Selection, Acquisition of Data and Comparison of Demographic and Clinical Data of Patients with Respect to the Status of Significant Dysmorphic Plasma Cells Presentation

Total 91 PCM patients diagnosed from January 2013 to December 2017 at author's institution were enrolled retrospectively. The presentation of dysmorphic features in the neoplastic PC in BM aspirates at diagnosis was retrospectively reviewed by two hematopathologists with more than 7 years of experiences in BM reading and the mean value was finally used. Total 40 (44.0%) patients showed the presence of dysmorphic PC with morphology such as binucleation, multinucleation, prominent nucleoli and irregular shape in the cytoplasm, with the frequency of more than 1% (median 5%, range 3–18%) among total PC. As a cutoff value for determining the presentation of significant dysmorphic PC (SDPC), the median value (5%) of dysmorphic PC presentation found in 40 patients (defined as SDPC5) and the pre-defined cutoff criteria (10%) used in the determination of significant dysplasia for MDS (defined as SDPC10) was applied in this study. Examples of PCM cases with typical PC morphology and SDPC are represented in the Fig. 1.

The demographic and clinical data of patients such as hemogram, serum-β2M, albumin and LDH levels, status of plasmablastic type (defined as the presence of plasmablasts $\geq$ 2% among total BM nucleated cells), R-ISS stage at diagnosis, performance of autologous hematopoietic stem cell transplantation (ASCT), death rates, total numbers and reduction of BM PC at diagnosis and each follow-up BM examination, type of serum/urine monoclonal gammopathy at diagnosis, the absolute amount and reduction of serum/urine monoclonal protein at diagnosis and each follow-up, results of karyotyping and FISH analysis at diagnosis, type of induction chemotherapy regimen were obtained from the retrospective review of electronic medical record, and were compared between two patient subgroups categorized with SDPC5 and SDPC10 presentation status. This study was approved by the Institutional Review Board of author's institution (Ulsan University Hospital, approval number: UUH20180516-HE005).

Comparison of Clinical Characteristics at Diagnosis Obtained from 91 Plasma Cell Myeloma Patients with Respect to Status of Total Plasma Cells at Diagnosis, Absolute Plasma Cell Reduction at 1st Follow-Up and Serum M-Protein Reduction at 1st Follow-Up

Clinical characteristics at diagnosis obtained from 91 PCM patients were compared between two patient subgroups categorized by three factors such as total BM PC (%) at diagnosis, absolute PC reduction at 1st follow-up and serum M-protein reduction at 1st follow-up. As a cutoff value of three factors, median values obtained from total 91 PCM patients (30.5% for absolute PC reduction at 1st follow-up, 37.7% for total BM PC at diagnosis and 1.16×10 g/L for absolute serum monoclonal protein reduction at 1st follow-up) were determined as each defining factor for the categorization of two patient subgroups.

Regression Analysis for the Identification of Independent Prediction Markers for Defining Specific Clinical and treatment Response Characteristics of Total 91 Plasma Cell Myeloma Patients

In these analysis, total BM PC (%) at diagnosis was selected as a representative factor for defining specific clinical and treatment response characteristics of PCM patients, as this factor showed statistically significant differences in the majority of clinical variables described above, between two patient subgroups categorized by this factor in the previous comparison analysis. In the multivariate logistic regression analysis, all variables with statistically significant differences between patients with total BM PC $\geq$ 37.7% and those with total BM PC $<$ 37.7% at diagnosis were included as covariates and *P* value of each variable was adjusted with all other covariates.

Statistical Analysis

Since all continuous variables showed normal distribution by the Kolmogorov–Sminorv test, mean values and

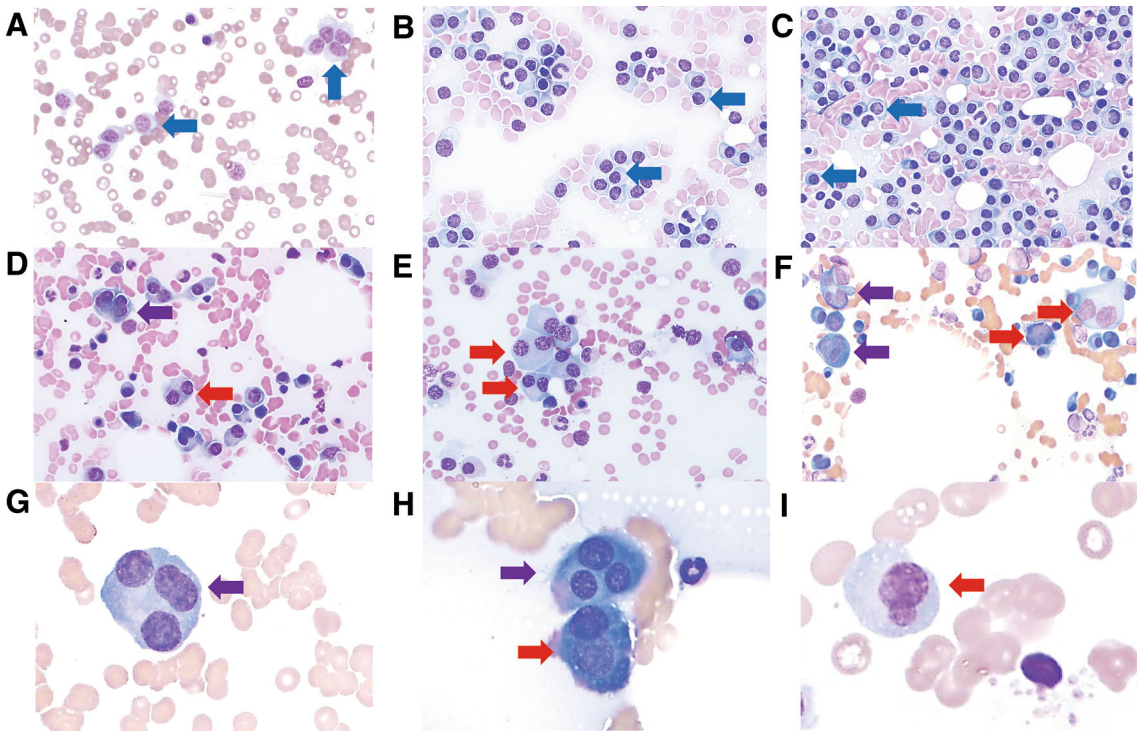

Fig. 1 Comparison of neoplastic plasma cells with typical morphology (**a**–**c**) and dysmorphic features (**d**–**i**) in bone marrow aspirates obtained from patients with plasma cell myeloma. Upper figures (**a**–**c**) show three cases with plasma cell myeloma presenting neoplastic plasma cells with typical morphology such as single, round, eccentric nucleus and perinuclear halo in the cytoplasm (indicated with blue colored arrows, Wright stain, X400) in bone marrow aspirates. Middle figures (**d**–**f**) show three cases with plasma cell myeloma presenting neoplastic plasma cells with dysmorphic features such as binucleation, prominent nucleoli and irregular shape in the cytoplasm (indicated with red colored arrows, Wright stain, X400) or multinucleation (indicated with purple colored arrows, Wright stain, X400) in bone marrow aspirates. Lower figures with high resolution (**g**–**i**) shows three cases with plasma cell myeloma presenting dysmophic plasma cells with binucleation and nuclear budding (indicated with red colored arrows, Wright stain, X1,000) or multinucleation (indicated with purple colored arrows, Wright stain, X1,000) in bone marrow aspirates

standard deviations were provided in all tables. Pearson chi-square or Fisher's exact tests (in cases with numbers < 5) were used to compare categorical variables and Student's t–test was used to compare continuous variables. For all analyses, tests were two-tailed and P values ≤ 0.05 were considered statistically significant. All statistical analyses were performed using the IBM SPSS software for Windows, version 21.0 (IBM Corp, Armonk, NY, USA).

Results

Comparison of Demographic and Clinical Characteristics at Diagnosis Obtained from 91 Plasma Cell Myeloma Patients with Respect to the Status of Significant Dysmorphic Plasma Cells Presentation

Among total 91 PCM patients, 36 (39.6%)/17 (18.7%) patients showed SDPC5/SDPC10 presentation at diagnosis, respectively. Patients with SDPC5 presentation harbored significantly more total BM PC at diagnosis ($P = 0.004$) than those without SDPC5 presentation, and showed significantly greater absolute PC reduction at 1st follow-up ($P = 0.007$) and at 2nd follow-up ($P = 0.047$) than those without SDPC5 presentation. Patients with SDPC5 presentation also showed significantly higher incidence of *CKS1B* gain at FISH analysis ($P = 0.022$) than those without SDPC5 presentation.

As for SDPC10, patients with SDPC10 presentation showed identical results with SDPC5, and they also showed significantly higher incidence of *RB1* loss at FISH analysis ($P = 0.032$) than those without SDPC10 presentation. However, other variables did not show statistically significant differences between two patient subgroups categorized by status of SDPC5/SDPC10 presentation at diagnosis (Table 1).

The most common dysmorphic features of patients with SDPC5/SDPC10 presentation was binucleation (88.9%/94.1%), followed by multinucleation (77.8%/82.4%), irregular shape in the cytoplasm (58.3%/58.8%), and prominent nucleoli (33.3%/35.3%) in the order of

Table 1 Comparison of clinical characteristics at diagnosis obtained from 91 plasma cell myeloma patients with respect to the status of dysmorphism in the neoplastic plasma cells

Variables	Dysmorphism < 5% (N = 55)	Dysmorphism ≥ 5% (N = 36)	*P* value	Dysmorphism < 10% (N = 74)	Dysmorphism ≥ 10% (N = 17)	*P* value
Sex (M:F)	36:19	18:18	0.142	45:29	29:8	0.551
Age (years)	67.62 ± 9.38	67.64 ± 11.78	0.993	67.19 ± 10.25	69.53 ± 10.78	0.403
WBC ($\times 10^9$/L)	5.50 ± 2.30	6.04 ± 3.95	0.409	5.64 ± 3.10	6.02 ± 2.90	0.643
Hb (× 10 g/L)	9.97 ± 2.18	9.35 ± 1.75	0.153	9.87 ± 2.13	9.10 ± 1.40	0.160
PLT ($\times 10^{12}$/L)	214.09 ± 75.84	210.72 ± 124.97	0.873	218.30 ± 100.53	188.65 ± 81.98	0.261
Beta-2-microglobulin ($\times 10^{-3}$ g/L)	7.97 ± 8.96	8.14 ± 5.97	0.924	8.24 ± 8.45	7.16 ± 4.73	0.615
Albumin (× 10 g/L)	3.54 ± 0.67	3.28 ± 0.59	0.057	3.48 ± 0.65	3.23 ± 0.57	0.143
LDH (IU/L)	297.75 ± 148.46	328.97 ± 233.83	0.437	323.80 ± 199.01	250.47 ± 99.74	0.144
Plasmablastic type (%)	17/55 (30.9)	17/36 (47.2)	0.116	27/74 (36.5)	7/17 (41.2)	0.719
R-ISS stage (1/2/3) (%)	10 (18.2)/31 (56.4)/14 (25.4)	3 (8.3)/21 (58.4)/12 (33.3)	0.374	11 (14.9)/43 (58.1)/20 (27.0)	2 (11.8)/9 (52.9)/6 (35.3)	0.783
Performance of ASCT (%)	16/55 (29.1)	12/36 (33.3)	0.668	22/74 (29.7)	6/17 (35.3)	0.654
Death (%)	10/55 (18.2)	9/36 (25.0)	0.434	15 /74 (20.3)	4/17 (23.5)	0.766
Total BM PC at diagnosis (%)	32.01 ± 23.38	46.28 ± 21.63	0.004	37.16 ± 25.06	44.78 ± 16.53	0.020
BM PC at 1st follow-up (%)	6.96 ± 16.88	7.00 ± 8.27	0.991	7.01 ± 15.15	6.80 ± 8.60	0.966
Absolute PC reduction at 1st follow-up (%)	23.79 ± 20.96	41.42 ± 25.06	0.007	29.99 ± 25.19	38.89 ± 18.57	0.034
Total BM PC at 2nd follow-up (%)	8.65 ± 16.10	6.21 ± 19.07	0.661	6.67 ± 14.30	5.07 ± 25.89	0.505
Absolute PC reduction at 2nd follow-up (%)	20.87 ± 27.15	40.34 ± 33.46	0.047	29.20 ± 31.24	37.00 ± 32.33	0.049
Total BM PC at 3rd follow-up (%)	4.67 ± 5.60	12.50 ± 18.42	0.178	8.47 ± 13.61	3.75 ± 0.35	0.637
Absolute PC reduction at 3rd follow-up (%)	35.04 ± 28.59	39.72 ± 34.18	0.736	35.60 ± 31.49	50.75 ± 13.78	0.516
Type of serum monoclonal gammopathy (%),			0.146 (overall)			0.488 (overall)
IgG kappa	23 (41.8)	14 (38.9)	0.781	31 (41.9)	6 (35.4)	0.617
IgG lambda	16 (29.1)	11 (30.5)	0.881	22 (29.7)	5 (29.4)	0.979
IgA kappa	3 (5.4)	4 (11.1)	0.428	4 (5.4)	3 (17.6)	0.118
IgA lambda	7 (12.7)	4 (11.1)	0.817	8 (10.8)	3 (17.6)	0.424
IgM kappa	0 (0.0)	1 (2.8)	0.396	1 (1.4)	0 (0.0)	0.813
Free kappa	0 (0.0)	2 (5.6)	0.154	2 (2.7)	0 (0.0)	0.660
Free lambda	6 (10.9)	0 (0.0)	0.078	6 (8.1)	0 (0.0)	0.589
Type of urine monoclonal gammopathy (%)			0.750 (overall)			0.708 (overall)
Free kappa	19 (34.5)	16 (44.4)	0.343	26 (35.1)	9 (52.9)	0.174
Free lambda	25 (45.5)	13 (36.1)	0.377	33 (44.7)	5 (29.4)	0.252
IgG kappa	6 (10.9)	5 (13.9)	0.670	9 (12.2)	2 (11.8)	0.664
IgG lambda	4 (7.3)	2 (5.6)	0.747	5 (6.8)	1 (5.9)	0.689

Table 1 continued

Variables	Dysmorphism < 5% (N = 55)	Dysmorphism ≥ 5% (N = 36)	*P* value	Dysmorphism < 10% (N = 74)	Dysmorphism ≥ 10% (N = 17)	*P* value
IgA kappa	1 (1.8)	0 (0.0)	0.416	1 (1.4)	0 (0.0)	0.813
Karyotype (%)			0.456 (overall)			0.503 (overall)
Normal	31 (56.4)	16 (44.4)	0.266	41 (55.4)	6 (35.3)	0.135
Complex	18 (32.7)	18 (50.0)	0.099	27 (36.5)	9 (52.9)	0.211
t(11;14)(q13;q32)	2 (3.6)	0 (0.0)	0.516	2 (2.7)	0 (0.0)	0.660
− 13/del(13q)	2 (3.6)	1 (2.8)	0.823	2 (2.7)	1 (5.9)	0.466
Others	2 (3.6)	1 (2.8)	0.823	2 (2.7)	1 (5.9)	0.466
FISH results (%)						
Normal	21 (38.2)	12 (33.3)	0.638	30 (40.5)	3 (17.6)	0.077
RB1 loss	20 (36.4)	13 (36.1)	0.980	23 (31.1)	10 (58.8)	0.032
TP53 loss	8 (14.5)	4 (11.1)	0.758	10 (13.5)	2 (11.8)	0.848
CKS1B gains	12 (21.8)	16 (44.4)	0.022	17 (23.0)	11 (64.7)	0.001
MAF rearrangements	9 (16.4)	3 (8.3)	0.268	10 (13.5)	2 (11.8)	0.848
FGFR3 rearrangements	8 (14.5)	4 (11.1)	0.758	9 (12.2)	3 (17.6)	0.547
CCND1 rearrangements	5 (9.1)	1 (2.8)	0.397	5 (6.8)	1 (5.9)	0.896
Induction chemotherapy regimen (%)			0.724 (overall)			0.335 (overall)
TD	10 (18.2)	8 (22.3)	0.636	16 (21.6)	2 (11.8)	0.508
VMP	32 (58.2)	18 (50.0)	0.443	42 (56.8)	8 (47.0)	0.469
VTD	11 (20.0)	7 (19.4)	0.948	13 (17.6)	5 (29.4)	0.269
RD	2 (3.6)	3 (8.3)	0.381	3 (4.2)	2 (11.8)	0.233

[†]Normal distribution of all continuous variables was confirmed from Kolmogorov–Smirnov test and mean values and standard deviations are represented in this table and *P* values were obtained from Pearson chi-square/Fisher's exact tests (for categorical variables) and Students' t-test (for continuous variables)

M male, *F* female, *SD* standard deviations, *WBC* white blood cells, *Hb* haemoglobin, *PLT* platelets, *LDH* lactate dehydrogenase, *R-ISS* revised international staging system for multiple myeloma, *ASCT* autologous stem cell transplantation, *BM* bone marrow, *PC* plasma cells, *FISH* fluorescence in situ hybridization, *TD* thalidomide-dexamethasone, *VMP* bortezomib-melphalan-prednisone, *VTD* bortezomib-thalidomide-dexamethasone, *RD* lenalidomide-dexamethasone

frequency. Significant association between SDPC5/SDPC10 presentations and PC infiltration pattern in BM biopsy, existence of BM fibrosis was not identified.

Comparison of Serum and Urine Monoclonal Protein Levels at Diagnosis and Each Follow-Up Data Obtained from 91 Plasma Cell Myeloma Patients with Respect to the Status of Significant Dysmorphic Plasma Cells Presentation

Serum monoclonal protein measured at diagnosis and each follow-up did not show significant differences between two patient subgroups. However, patients with SDPC5 presentation showed significantly greater absolute serum monoclonal protein reduction at 1st follow-up ($P = 0.041$) and at 2nd follow-up ($P = 0.039$) than those without SDPC5 presentation. However, when follow-up interval was integrated, all comparisons did not show statistically significant differences. In the urine monoclonal proteins, all results did not show statistically significant differences between two patient subgroups. Results of SDPC10 presentation was also identical with SDPC5 (Table 2).

Comparison of Clinical Characteristics at Diagnosis Obtained from 91 Plasma Cell Myeloma Patients with Respect to Status of Total Plasma Cells at Diagnosis, Absolute Plasma Cell Reduction at 1st Follow-Up and Serum M-Protein Reduction at 1st Follow-Up

Patients with absolute PC reduction ≤ 30.5% at 1st follow-up BM examination showed significantly less total BM PC

Table 2 Comparison of serum and urine M-protein levels at diagnosis and each follow-up data obtained from 91 plasma cell myeloma patients with respect to the status of dysmorphism in the neoplastic plasma cells

Variables	Dysmorphism < 5% (N = 55)	Dysmorphism ≥ 5% (N = 36)	*P* value	Dysmorphism < 10% (N = 74)	Dysmorphism ≥ 10% (N = 17)	*P* value
Serum						
M-protein at diagnosis (× 10 g/L)	2.89 ± 2.07	3.53 ± 2.09	0.154	3.06 ± 2.07	3.53 ± 2.22	0.405
M-protein at 1st follow-up (× 10 g/L)	1.57 ± 1.43	1.56 ± 1.25	0.965	1.56 ± 1.41	1.61 ± 1.10	0.900
Absolute M-protein reduction at 1st follow-up (× 10 g/L)	1.36 ± 1.41	2.02 ± 1.85	0.041	1.53 ± 1.60	1.96 ± 1.70	0.044
Absolute M-protein reduction/follow-up interval at 1st follow-up (× 10 g/L/days)	0.045 ± 0.042	0.062 ± 0.058	0.130	0.050 ± 0.050	0.059 ± 0.045	0.516
M-protein at 2nd follow-up (× 10 g/L)	1.08 ± 1.13	1.01 ± 0.91	0.782	1.08 ± 1.11	0.98 ± 0.80	0.752
Absolute M-protein reduction at 2nd follow-up (× 10 g/L)	1.75 ± 1.73	2.77 ± 2.24	0.039	2.00 ± 1.97	2.74 ± 2.07	0.049
Absolute M-protein reduction/follow-up interval at 2nd follow-up (× 10 g/L/days)	0.024 ± 0.025	0.039 ± 0.035	0.056	0.029 ± 0.031	0.036 ± 0.027	0.408
M-protein at 3rd follow-up (× 10 g/L)	0.94 ± 0.98	0.84 ± 0.80	0.652	0.95 ± 0.94	0.76 ± 0.75	0.495
Absolute M-protein reduction at 3rd follow-up (× 10 g/L)	2.05 ± 1.84	2.95 ± 2.23	0.085	2.28 ± 2.05	2.98 ± 2.04	0.266
Absolute M-protein reduction/follow-up interval at 3rd follow-up (× 10 g/L/days)	0.018 ± 0.017	0.028 ± 0.024	0.070	0.021 ± 0.021	0.026 ± 0.019	0.404
M-protein at 4th follow-up (× 10 g/L)	0.84 ± 0.98	0.84 ± 0.96	0.983	0.87 ± 0.97	0.75 ± 0.98	0.706
Absolute M-protein reduction at 4th follow-up (× 10 g/L)	2.27 ± 1.96	2.92 ± 2.14	0.232	2.45 ± 2.12	2.92 ± 1.83	0.473
Absolute M-protein reduction/follow-up interval at 4th follow-up (× 10 g/L/days)	0.015 ± 0.014	0.021 ± 0.019	0.154	0.017 ± 0.016	0.019 ± 0.015	0.626
Urine						
M-protein at diagnosis ($\times 10^{-3}$ g/day)	448.71 ± 914.22	482.91 ± 1046.52	0.870	501.92 ± 1034.45	289.54 ± 544.88	0.415
M-protein at 1st follow-up ($\times 10^{-3}$ g/day)	156.35 ± 491.15	164.53 ± 588.97	0.943	194.95 ± 581.34	5.63 ± 14.27	0.185
Absolute M-protein reduction at 1st follow-up ($\times 10^{-3}$ g/day)	382.86 ± 1129.44	395.24 ± 678.89	0.958	385.01 ± 1025.39	402.19 ± 619.56	0.956
Absolute M-protein reduction/follow-up interval at 1st follow-up ($\times 10^{-3}$ g/day/days)	12.98 ± 47.68	12.39 ± 24.27	0.952	13.33 ± 42.92	9.80 ± 15.66	0.780
M-protein at 2nd follow-up ($\times 10^{-3}$ g/day)	144.34 ± 574.67	21.27 ± 59.84	0.264	120.40 ± 505.64	3.98 ± 10.15	0.378
Absolute M-protein reduction at 2nd follow-up ($\times 10^{-3}$ g/day)	516.26 ± 1331.37	371.05 ± 774.15	0.641	459.37 ± 1223.54	440.21 ± 635.55	0.960

Table 2 continued

Variables	Dysmorphism < 5% (N = 55)	Dysmorphism ≥ 5% (N = 36)	*P* value	Dysmorphism < 10% (N = 74)	Dysmorphism ≥ 10% (N = 17)	*P* value
Absolute M-protein reduction/follow-up interval at 2nd follow-up ($\times 10^{-3}$ g/day/days)	8.54 ± 28.65	4.35 ± 8.99	0.502	7.21 ± 24.99	5.11 ± 7.48	0.785
M-protein at 3rd follow-up ($\times 10^{-3}$ g/day)	94.13 ± 264.67	54.13 ± 213.85	0.516	99.44 ± 273.73	1.76 ± 5.38	0.174
Absolute M- protein reduction at 3rd follow-up ($\times 10^{-3}$ g/day)	559.24 ± 1211.64	376.45 ± 795.56	0.537	486.08 ± 1131.76	443.08 ± 633.55	0.905
Absolute M-protein reduction/follow-up interval at 3rd follow-up ($\times 10^{-3}$ g/day/days)	5.74 ± 13.47	2.96 ± 6.01	0.363	4.75 ± 11.91	3.52 ± 5.04	0.741
M-protein at 4th follow-up ($\times 10^{-3}$ g/day)	42.65 ± 119.47	61.46 ± 272.35	0.722	66.21 ± 228.29	1.50 ± 4.91	0.296
Absolute M-protein reduction at 4th follow-up ($\times 10^{-3}$ g/day)	636.46 ± 1248.44	397.04 ± 807.23	0.444	539.10 ± 1155.94	479.70 ± 655.32	0.877
Absolute M-protein reduction/follow-up interval at 4th follow-up ($\times 10^{-3}$ g/day/days)	4.66 ± 9.53	2.35 ± 4.43	0.303	3.76 ± 8.36	3.01 ± 4.17	0.786

†Normal distribution of all continuous variables was confirmed from Kolmogorov–Smirnov test and mean values and standard deviations are represented and in this table and *P* values were obtained Students' t-test

M monoclonal

at diagnosis ($P < 0.001$) than those with absolute PC reduction > 30.5% at 1st follow-up BM examination. However, patients with absolute PC reduction ≤ 30.5% at 1st follow-up BM examination showed significantly higher incidences of normal karyotype at karyotyping ($P < 0.001$), normal results at FISH analysis ($P = 0.005$), and R-ISS stage 1 ($P = 0.031$) than those with absolute PC reduction > 30.5% at 1st follow-up BM examination. Patients with absolute PC reduction ≤ 30.5% at 1st follow-up BM examination also showed significantly lower incidences of complex karyotype at karyotyping ($P = 0.002$) and R-ISS stage 3 ($P = 0.007$) than those with absolute PC reduction > 30.5% at 1st follow-up BM examination. In 24 patients with absolute PC reduction > 30.5% at 1st follow-up, only two patients showed BM PC < 37.7% at diagnosis and these two patients did not show SDPC5/SDPC10 presentation. In 55 patients without SDPC5/SDPC10 presentation, there were seven cases with complex karyotype and absolute PC reduction > 30.5% at 1st follow-up.

Patients with total BM PC ≥ 37.7% at diagnosis showed significantly higher incidences of complex karyotype at karyotyping ($P = 0.013$), *RB1* loss ($P = 0.007$) and *FGFR3* rearrangements ($P = 0.032$) at FISH analysis, R-ISS stage 3 ($P = 0.014$), SDPC5/SDPC10 presentation ($P = 0.003$/0.019) and plasmablastic type ($P = 0.013$) than those with total BM PC < 37.7% at diagnosis. Patients with total BM PC ≥ 37.7% at diagnosis also showed significantly lower incidences of normal karyotype at karyotyping ($P = 0.002$), normal results at FISH analysis ($P = 0.003$) and R-ISS stage 1 ($P = 0.005$) than those with total BM PC < 37.7% at diagnosis.

Patients with serum monoclonal protein reduction ≤ 1.16 × 10 g/L at 1st follow-up showed significantly higher incidence of *MAF* rearrangements at FISH analysis ($P = 0.003$) than those with serum monoclonal protein reduction > 1.16 × 10 g/L at 1st follow-up, but other variables did not show statistically significant differences between two patient subgroups categorized by degree of serum monoclonal protein reduction at 1st follow-up (Table 3).

Regression Analysis for the Identification of Independent Prediction Markers for Defining Specific Clinical and Treatment Response Characteristics of Total 91 Plasma Cell Myeloma Patients

In the univariate analysis, variables with significant differences between patients with total BM PC ≥ 37.7% at diagnosis and those with total BM PC < 37.7% at diagnosis were included for univariate logistic regression analysis. Both presence of normal karyotype at karyotyping and normal results in FISH analysis at diagnosis were statistically

Table 3 Comparison of clinical characteristics at diagnosis obtained from 91 plasma cell myeloma patients with respect to status of total plasma cells at diagnosis, absolute plasma cell reduction at 1st follow-up and serum M-protein reduction at 1st follow-up

Variables	Absolute PC reduction (%) at 1st follow-up			Total BM PC (%) at diagnosis			Serum M-protein reduction (× 10 g/L) at 1st follow-up		
	> 30.5 (G)	≤ 30.5 (P)	*P* value	< 37.7 (G)	≥ 37.7 (P)	*P* value	> 1.16 (G)	≤ 1.16 (P)	*P* value
Sex (M:F)	13:11	19:12	0.595	31:19	23:18	0.568	26:20	26:16	0.608
Age. mean ± SD	62.21 ± 7.35	65.74 ± 10.21	0.159	68.48 ± 10.37	66.59 ± 10.31	0.387	66.48 ± 9.28	69.74 ± 11.01	0.136
Total BM PC at diagnosis (%), mean ± SD	58.69 ± 15.91	21.08 ± 14.22	< 0.001	18.87 ± 9.37	60.55 ± 13.12	< 0.001	40.85 ± 24.05	34.11 ± 23.17	0.185
Karyotype results (%)									
Normal	4/24 (16.7)	21/31 (67.7)	< 0.001	33/50 (66.0)	14/41 (34.1)	0.002	23/46 (50.0)	22/42 (52.4)	0.823
Complex	16/24 (61.5)	8/31 (25.8)	0.002	14/50 (28.0)	22/41 (53.7)	0.013	19/46 (41.3)	16/42 (38.1)	0.759
t(11;14)(q13;q32)	1/24 (4.1)	1/31 (3.2)	0.853	1/50 (2.0)	1/41 (2.4)	0.887	1/46 (2.2)	1/42 (2.4)	0.948
− 13/del(13q)	3/24 (12.5)	0/31 (0.0)	0.077	1/50 (2.0)	2/41 (4.9)	0.587	2/46 (4.3)	1/42 (2.4)	0.612
FISH results (%)									
Normal	4/24 (16.7)	17/31 (54.8)	0.005	25/50 (50.0)	8/41 (19.5)	0.003	15/46 (32.6)	18/42 (42.9)	0.321
RB1 loss	12/24 (50.0)	8/31 (25.8)	0.064	12/50 (24.0)	21/41 (51.2)	0.007	18/46 (39.1)	12/42 (28.6)	0.297
TP53 loss	5/24 (20.8)	3/31 (9.7)	0.245	5/50 (10.0)	7/41 (17.1)	0.321	8/46 (17.4)	3/42 (7.1)	0.147
CKS1B gains	8/24 (33.3)	7/31 (22.6)	0.375	12/50 (24.0)	16/41 (39.0)	0.122	15/46 (32.6)	12/42 (28.6)	0.682
MAF rearrangements	3/24 (12.5)	2/31 (6.5)	0.643	6/50 (12.0)	6/41 (14.6)	0.712	1/46 (2.2)	10/42 (23.8)	0.003
FGFR3 rearrangements	5/24 (20.8)	2/31 (6.5)	0.220	3/50 (6.0)	9/41 (22.0)	0.032	8/46 (17.4)	4/42 (9.5)	0.359
CCND1 rearrangements	1/24 (4.1)	2/31 (6.5)	0.711	3/50 (6.0)	3/41 (7.3)	0.801	3/46 (6.5)	2/42 (4.8)	0.722
PC dysmorphism ≥ 5% (%)	12/24 (50.0)	9/31 (29.0)	0.112	13/50 (26.0)	23/41 (56.1)	0.003	21/46 (45.7)	14/42 (33.3)	0.238
PC dysmorphism ≥ 10% (%)	5/24 (20.8)	5/31 (16.1)	0.654	5/50 (10.0)	12/41 (29.3)	0.019	11/46 (23.9)	5/42 (11.9)	0.145
Plasmablastic type (%)	14/24 (58.3)	10/31 (32.3)	0.053	13/50 (26.0)	21/41 (51.2)	0.013	17/46 (37.0)	16/42 (38.1)	0.912
Induction CTx regimen (%)			0.280 (Overall)			0.249 (Overall)			0.067 (Overall)
TD	5/24 (20.8)	6/31 (19.4)	0.892	13/50 (26.0)	5/41 (12.2)	0.100	5/46 (10.9)	11/42 (26.2)	0.063
VMP	11/24 (45.8)	20/31 (64.5)	0.166	27/50 (54.0)	23/41 (56.1)	0.841	26/46 (56.5)	26/42 (61.9)	0.608
VTD	8/24 (33.3)	5/31 (16.1)	0.136	7/50 (14.0)	11/41 (26.8)	0.126	11/46 (23.9)	4/42 (9.5)	0.092
RD	0/24 (0.0)	0/31 (0.0)	NA	3/50 (6.0)	2/41 (4.9)	0.815	4/46 (8.7)	1/42 (2.4)	0.363
R-ISS stage (%)			0.008 (Overall)			0.003 (Overall)			0.410 (Overall)
1	1/24 (4.1)	9/31 (29.0)	0.031	12/50 (24.0)	1/41 (2.4)	0.005	9/46 (19.6)	4/42 (9.5)	0.236
2	10/24 (41.7)	16/31 (51.6)	0.464	29/50 (58.0)	23/41 (56.1)	0.855	25/46 (54.3)	25/42 (59.5)	0.624
3	13/24 (54.2)	6/31 (19.4)	0.007	9/50 (18.0)	17/41 (41.5)	0.014	12/46 (26.1)	13/42 (31.0)	0.613

[†]Normal distribution of all continuous variables was confirmed from Kolmogorov–Smirnov test and mean values and standard deviations are represented in this table and *P* values were obtained from Pearson chi-square/Fisher's exact tests (for categorical variables) and Students' t-test (for continuous variables)

M male, *F* female, *FISH* fluorescence in situ hybridization, *PC* plasma cells, *CTx* chemotherapy, *TD* thalidomide-dexamethasone, *VMP* bortezomib-melphalan-prednisone, *VTD* bortezomib-thalidomide-dexamethasone, *RD* lenalidomide-dexamethasone, *R-ISS* revised international staging system for multiple myeloma, *BM* bone marrow, *SD* standard deviation, *G* good, *P* poor

Table 4 Univariate and multivariate logistic regression analysis for the identification of independent prediction marker for the presence of total bone marrow plasma cells ≥ 37.7% at diagnosis of plasma cell myeloma

	Total bone marrow plasma cells ≥ 37.7% at diagnosis		
	HR (95% CI)	*P* value	Interpretation
Univariate analysis, variables			
Normal karyotype (vs. no)	0.267 (0.112–0.638)	0.003	Predictor of BM PC < 37.7% at diagnosis if normal karyotype (+)
Complex karyotype (vs. no)	2.977 (1.247–7.111)	0.014	Predictor of BM PC ≥ 37.7% at diagnosis if complex karyotype (+)
Normal at FISH analysis (vs. no)	0.242 (0.094–0.627)	0.003	Predictor of BM PC < 37.7% at diagnosis if normal at FISH analysis (+)
RB1 loss (+) at FISH analysis (*vs*. no)	3.325 (1.362–8.116)	0.008	Predictor of BM PC ≥ 37.7% at diagnosis if *RB1* loss at FISH analysis (+)
FGFR3 rearrangements (+) at FISH analysis (vs. no)	4.406 (1.107–17.544)	0.035	Predictor of BM PC ≥ 37.7% at diagnosis if *FGFR3* rearrangements at FISH analysis (+)
Dysmorphic plasma cells ≥ 5% in BM at diagnosis (vs. no)	3.637 (1.504–8.795)	0.004	Predictor of BM PC ≥ 37.7% at diagnosis if dysmorphic PC ≥ 5% in BM at diagnosis (+)
Dysmorphic plasma cells ≥ 10% in BM at diagnosis (vs. no)	2.982 (1.279–5.780)	0.011	Predictor of BM PC ≥ 37.7% at diagnosis if dysmorphic PC ≥ 10% in BM at diagnosis (+)
Plasmablastic type (+) at diagnosis (vs. no)	2.988 (1.240–7.205)	0.015	Predictor of BM PC ≥ 37.7% at diagnosis if plasmablastic type at diagnosis (+)
R-ISS stage 2 at diagnosis (*vs*. stage 1)	9.517 (1.151–78.667)	0.037	Predictor of BM PC ≥ 37.7% at diagnosis if R-ISS stage 2 at diagnosis (+)
R-ISS stage 3 at diagnosis (vs. stage 1)	22.617 (2.526–203.378)	0.005	Predictor of BM PC ≥ 37.7% at diagnosis if R-ISS stage 3 at diagnosis (+)
Multivariate analysis, variables			
Normal karyotype (vs. no)	0.203 (0.025–1.671)	0.138	NS
Complex karyotype (vs. no)	0.124 (0.012–1.297)	0.081	NS
Normal at FISH analysis (vs. no)	0.527 (0.128–2.163)	0.374	NS
RB1 loss (+) at FISH analysis (*vs*. no)	1.948 (0.505–7.517)	0.333	NS
FGFR3 rearrangements (+) at FISH analysis (vs. no)	3.202 (0.590–17.373)	0.177	NS
Dysmorphic plasma cells ≥ 5% in BM at diagnosis (vs. no)	4.649 (1.582–13.663)	0.005	Independent predictor of BM PC ≥ 37.7% at diagnosis if dysmorphic PC ≥ 5% in BM at diagnosis (+)
Dysmorphic plasma cells ≥ 10% in BM at diagnosis (vs. no)	2.613 (1.155–8.720)	0.039	Independent predictor of BM PC ≥ 37.7% at diagnosis if dysmorphic PC ≥ 10% in BM at diagnosis (+)
Plasmablastic type (+) at diagnosis (vs. no)	2.489 (0.803–7.717)	0.114	NS
R-ISS stage 2 at diagnosis (*vs*. stage 1)	16.833 (1.396–202.969)	0.026	Independent predictor of BM PC ≥ 37.7% at diagnosis if R-ISS stage 2 at diagnosis (+)
R-ISS stage 3 at diagnosis (vs. stage 1)	32.733 (2.139–500.877)	0.012	Independent predictor of BM PC ≥ 37.7% at diagnosis if R-ISS stage 3 at diagnosis (+)

[†]*P* values were obtained from multivariate logistic regression analysis with covariates including karyotype, FISH results, status of dysmorphic plasma cells at diagnosis, status of plasmablastic type at diagnosis and R-ISS stage at diagnosis

HR hazard ratio, *CI* confidence interval, *FISH* fluorescence in situ hybridization, *BM* bone marrow, *R-ISS* revised international staging system for multiple myeloma, *PC* plasma cells, *NS* not significant

significant predictors of total BM PC < 37.7% at diagnosis ($P = 0.003$ in both, respectively). In contrast, presence of complex karyotype at karyotyping, *RB1* loss at FISH analysis, *FGFR3* rearrangements at FISH analysis, SDPC5/SDPC10 presentation at diagnosis, plasmablastic type at diagnosis, R-ISS stage 2/3 were statistically significant predictors of total

BM PC $\geq$ 37.7% at diagnosis (P = 0.014, 0.008, 0.035, 0.004/0.011, 0.015, 0.037/0.005, respectively).

In the multivariate analysis, only three out of nine variables included in the previous univariate analysis, were found to be an independent predictor of total BM PC $\geq$ 37.7% at diagnosis with statistical significances when all other variables were adjusted. These three variables included SDPC5 presentation (P = 0.005), R-ISS stage 2 (P = 0.026) and R-ISS stage 3 (P = 0.012) at diagnosis. SDPC10 presentation were also found to be an independent predictor of total BM PC $\geq$ 37.7% at diagnosis with statistical significances (P = 0.039) when all other variables were adjusted (Table 4).

Discussion

Our study found that PCM patients with SDPC5/SDPC10 presentation show significantly more BM PC at diagnosis and higher incidence of *CKS1B* gain indicating 1q gains at diagnosis than those without SDPC5/SDPC10 presentation. Our study also identified that PCM patients with SDPC10 presentation show significantly higher incidence of *RB1* loss indicating 13q14 loss at diagnosis than those without SDPC10 presentation. These two abnormalities are poor prognostic indicators in PCM [1, 3–5] and these results indicate that SDPC5/SDPC10 presentation in PCM patients may be associated with poor prognosis in PCM caused from more BM PC to be removed and high incidences of 1q gains and 13q14 loss at diagnosis.

However, our study found that PCM patients with SDPC5/SDPC10 presentation show significantly greater absolute PC reduction at 1st and 2nd follow-up BM examinations, and also show significantly greater absolute serum monoclonal protein reductions at 1st and 2nd follow-up after induction chemotherapy than those without SDPC5/SDPC10 presentation. These results may suggest a speculation that PCM patients with SDPC5/SDPC10 presentation show good treatment response to induction chemotherapy although they show more BM PC and higher incidences of 1q gains and 13q14 loss at diagnosis than those without SDPC5/SDPC10 presentation.

In contrast to absolute PC and serum monoclonal protein reductions at 1st follow-up, in our study we found that more BM PC measured at diagnosis shows consistent association with poor prognosis such as high incidence of complex karyotype, presence of *RB1* loss and *FGFR3* rearrangements, plasmablastic type and R-ISS stage 3 at diagnosis. Our study also found that patients with more BM PC measured at diagnosis show higher incidence of SDPC5/SDPC10 presentation than those with less BM PC measured at diagnosis but absolute PC or serum monoclonal protein reductions at 1st follow-up after chemotherapy do not significantly correlate with SDPC5/SDPC10 presentation. These results support speculation of our study that more BM PC at diagnosis would be a poor prognostic indicator associated with SDPC5/SDPC10 presentation at diagnosis of PCM. Associations between great PC or serum monoclonal protein reductions after chemotherapy and high incidence of SDPC presentation should be addressed in more comprehensive study.

Our study identified that SDPC5/SDPC10 presentation at diagnosis would be an independent predictor of more BM PC at diagnosis, as well as high R-ISS stage. These results furtherly confirm that SDPC5/SDPC10 presentation would be correlated with more BM PC at diagnosis indicating poor prognosis, as well as high R-ISS stage. Therefore, we can suggest that the evaluation of SDPC5/SDPC10 presentation status would be useful in the prediction of prognosis in patients with PCM.

Although our study showed that patients treated with VMP regimen would show greater absolute PC reduction at 1st follow-up compared to other regimens, there was no statistical significance in the association of regimen type and absolute PC reduction status at 1st follow-up and there were also no significant association between regimen type and SDPC5/SDPC10 presentation status.

Our study has significant limitation regarding interpretation of study results raised from retrospective, single-center study design and small number of enrolled patients. These limitations may result in weak statistical power and therefore, prospective and multicenter study with more enrolled patients should be required to confirm suggestions and speculations raised from our present study.

In conclusion, our study demonstrated that SDPC presentation would be an independent predictor of more BM PC at diagnosis in PCM patients. Associations between SDPC presentation and higher incidence of *CKS1B* gains and *RB1* loss, greater PC/serum monoclonal protein reductions after chemotherapy were also identified. Association between SDPC presentation and favorable treatment response should be evaluated in more comprehensive study.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animal performed by any of the authors.

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