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Cytological-Pathologic Correlation

The diagnostic utility and frequency of CD56 expression in plasma cell myeloma

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ABSTRACT

Plasma cell myeloma (PCM) is a hematological malignancy characterized by systemic proliferation of neoplastic plasma cells within the bone marrow. Diagnosis requires clinical findings and immunohistochemical staining, including CD138, CD79a, cyclin D1, immunoglobulin κ (Igκ), and λ (Igλ). However, CD79a and cyclin D1 have limited sensitivity and specificity, and Igκ/Igλ assessment is often difficult due to overstaining. Therefore, more reliable antibodies are needed to accurately diagnose PCM. In this study, we examined the diagnostic utility of CD56 expression in PCM. We retrospectively performed immunostaining for CD138, CD56, CD79a, cyclin D1, Igκ, and Igλ in bone marrow samples from 116 patients with PCM.

CD56 expression was observed in 85/116 cases (73.3 %), CD79a was downregulated in 46/116 cases (39.7 %), and cyclin D1 expression was observed in 42/116 cases (36.2 %). The expression of CD56 was significantly higher than that of CD79a and cyclin D1 (both $p < 0.001$). The combination of two antibodies resulted in the highest detection rate when combining CD56 and CD79a (105/116, 90.5 %), which was significantly higher than the detection rates of CD56 and cyclin D1 (93/116, 80.2 %) and CD79a and cyclin D1 (75/116, 64.7 %) (both $p < 0.001$). In contrast, lymphoplasmacytic lymphoma and marginal zone lymphoma lacked CD56 and cyclin D1 expression. Furthermore, in cases where light chain restriction was undetectable (11/116, 9.5 %), all could be diagnosed as PCM based on CD56, CD79a, and cyclin D1. Among these, CD56 showed the highest detection rate (8/11, 72.7 %).

These findings highlight CD56 as a helpful marker for PCM diagnosis and support further clinical research.

1. Introduction

Plasma cell myeloma (PCM) is a hematological malignancy characterized by the proliferation of neoplastic plasma cells primarily within the bone marrow. It accounts for approximately 10 % of all hematologic neoplasms [1]. This disease is characterized by the presence of monoclonal (M) proteins produced by neoplastic plasma cells, which are detectable in the blood and/or urine, and is associated with end-organ manifestations caused by various bioactive substances. Epidemiologically, PCM constitutes approximately 1 % of all malignant tumors and causes approximately 20 % of deaths owing to hematologic malignancies [1,2].

The diagnostic criteria for PCM include clinical and pathological findings based on a comprehensive evaluation of bone marrow examinations, blood tests, imaging tests, and flow cytometry. Identification of neoplastic plasma cells in the bone marrow is essential, making immunohistochemical staining a critical component of the diagnostic process [2,3]. Common antibodies used to detect neoplastic plasma cells include CD79a, cyclin D1, Igκ, and Igλ. CD79a is widely expressed from precursor B cells to plasma cells; however, its downregulation has been observed in approximately 50 % of PCM cases [3]. Cyclin D1, which is expressed in mantle cell lymphoma, is dysregulated in 20–30 % of PCM cases [4]. Immunostaining for Igκ and Igλ is commonly used to assess light chain restriction; however, in some cases, interpretation is challenging owing to overstaining of background or decreased antigen expression. Therefore, immunostaining markers capable of accurately detecting neoplastic plasma cells in PCM are required.

CD56 is not expressed in reactive plasma cells but has been reported

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to be specifically expressed in PCM [5-11]. Furthermore, because CD56 is expressed in neoplastic plasma cells, it is helpful in distinguishing PCM from monoclonal gammopathy of undetermined significance, a premalignant plasma cell disorder [7,10]. Although CD56 is expected to be a helpful marker for the pathological diagnosis of PCM, no previous studies have examined its utility in combination with existing antibodies. In this study, we analyzed the expression of CD56 in PCM and its correlation with clinical parameters to evaluate its diagnostic utility. Additionally, comparative analyses were conducted with lymphomas that may contain neoplastic plasmacytic cells, such as bone marrow involvement in lymphoplasmacytic lymphoma (LPL) and marginal zone lymphoma (MZL).

2. Materials and methods

2.1. Patients, samples, and clinical data

This study included bone marrow biopsy or clot specimens from 116 patients diagnosed with PCM at Okayama University Hospital between 1997 and 2021. All PCM cases met the diagnostic criteria established by the International Myeloma Working Group [1]. For comparison, bone marrow biopsy or clot specimens from seven cases of LPL diagnosed between 2015 and 2022 and eight cases of MZL diagnosed between 2001 and 2018 were examined.

2.2. Immunohistochemical staining

Formalin-fixed paraffin-embedded tissue blocks were prepared from all specimens using 10 % neutral-buffered formalin, and 3 μm-thick sections were stained with hematoxylin and eosin (H&E). For PCM cases, immunohistochemical staining was performed for CD138 (MI15, 1:200, DAKO, Glostrup, Denmark), cyclin D1 (SP4, 1:75, Nichirei, Tokyo, Japan), CD56 (1B6, 1:20, Nichirei), CD79a (JCB117, 1:100, DAKO), Igκ (1:5, DAKO), and Igλ (1:10, DAKO). Igκ and Igλ were evaluated by in situ hybridization (ISH) in 19 cases. In LPL and MZL cases, immunohistochemical staining was performed for CD138, CD56, CD79a, and cyclin D1.

All immunostaining procedures were performed using an automated immunostainer (BOND-III; Leica Microsystems GmbH, Wetzlar, Germany) or VENTANA Benchmark (Roche, Basel, Switzerland).

All specimens were evaluated using H&E to identify clusters of plasma cells, and immunohistochemical findings were evaluated for these cell populations (Fig. 1). CD56 and cyclin D1 were considered positive when ≥30 % of CD138-positive cells exhibited expression; cases with <30 % were considered negative. Since these proteins are also expressed in normal cells, making differentiation difficult, we performed the evaluation using a higher cut-off value than previously reported [12]. CD79a expression was considered downregulated if it was <80 %, and positive if it was ≥80 %, using the same CD138-positive cell population as a reference.

Light chain restriction was determined by comparing Igκ- and Igλ-stained sections obtained by immunohistochemical staining or ISH. A case was considered to show light-chain restriction when there was more than a 10-fold difference in the number of positive plasma cells between the two stains. If no difference was observed, the case was classified as negative for light-chain restriction. Cases in which the detection of plasma cells were impossible owing to the background from diffusion of dyes or when no positive cells were observed were classified as undetermined (U.D.).

2.3. Statistical analysis

Statistical analysis was performed using Fisher's exact test with the Bonferroni correction. Quantitative data were expressed as percentages, and laboratory data were expressed as medians (ranges). Comparisons of CD56 expression with age or clinical information were performed using independent *t*-tests. Comparisons between the expression of CD56 and that of CD138, CD79a, and cyclin D1, as well as other clinical parameters, were performed using either the chi-square test or Fisher's exact test, depending on the sample size. All statistical analyses were conducted using R version 4.2.1, and a p-value of <0.05 was considered statistically significant.

3. Results

3.1. Immunohistochemical staining

The results of immunohistochemical staining of PCM are summarized in Table 1. CD138 expression was observed in 115 of 116 cases (99.1 %). CD56 was expressed in 85 of 116 cases (73.3 %), and CD79a in 70 of 116 cases (60.3 %), with downregulation noted in 46 cases (39.7 %). Cyclin D1 expression was identified in 42 of 116 cases (36.2 %), whereas 74 cases (63.8 %) showed no expression. A comparative analysis of each marker revealed that the expression rate of CD56 was significantly higher than that of CD79a and cyclin D1 (both $p < 0.001$). Light chain restriction was detected in 105 of 116 cases (90.5 %) in which evaluation was possible. Eleven cases were classified as U.D. because of background overstaining. All included cases were based on immunohistochemical staining and did not include ISH.

Table 2 shows details of cases categorized as U.D. for light chain restriction. All cases could be diagnosed as PCM using either CD56, CD79a, or cyclin D1 markers. The PCM detection rates were 4/11 cases (36.4 %) for CD79a, 8/11 cases (72.7 %) for CD56, and 3/11 cases (27.3 %) for cyclin D1, with CD56 showing the highest detection rate.

3.2. CD56 expression and clinical information

The association between CD56 expression and clinical features of PCM was evaluated (Table 3). In the CD56-positive group, there was a tendency toward the presence of serum-free light chains, urinary Bence Jones protein, and elevated serum β2-microglobulin levels; however, none of these differences were statistically significant ($p = 0.161$, $p = 0.158$, and $p = 0.114$, respectively). Additionally, there were no significant differences between the CD56-positive and CD56-negative groups with respect to the clinical manifestations typical of PCM (hypercalcemia, renal impairment, anemia, and bone lesions [CRAB]).

3.3. Optimization of antibody combinations for PCM diagnosis

The number of cases in which each antibody was detectable in the PCM is shown in Fig. 2A. There were 108/116 cases of PCM (93.1 %) detectable by CD56, CD79a, or cyclin D1. Consequently, only eight cases (6.9 %) were undetectable using all three antibodies. In addition, tumor plasma cells were detected using all antibodies in four cases (3.5 %).

To ensure accurate diagnosis of PCM, combinations of immunohistochemical markers with higher diagnostic values were evaluated (Fig. 2B). The combination of the two antibodies was examined, and 105 cases (90.5 %) of PCM were identified using a combination of CD56 and CD79a. A combination of CD56 and cyclin D1 was identified in 93 cases (80.2 %), whereas that of CD79a and cyclin D1 was identified in 75 cases (64.7 %). Comparison of the detection of each marker combination revealed that both CD56/CD79a and CD56/cyclin D1 had significantly higher detection rates than CD79a/cyclin D1 ($p < 0.0001$ and $p < 0.05$, respectively). There was no significant difference between the detection rates of CD56/CD79a and CD56/cyclin D1 ($p = 0.12$). A summary of the immunohistochemical findings is presented in Fig. 2. The detection rates of CD79a and cyclin D1 were nearly equivalent; however, only 12 cases (12.1 %) were positive for both markers, indicating that CD79a and cyclin D1 had expression patterns independent of CD56.

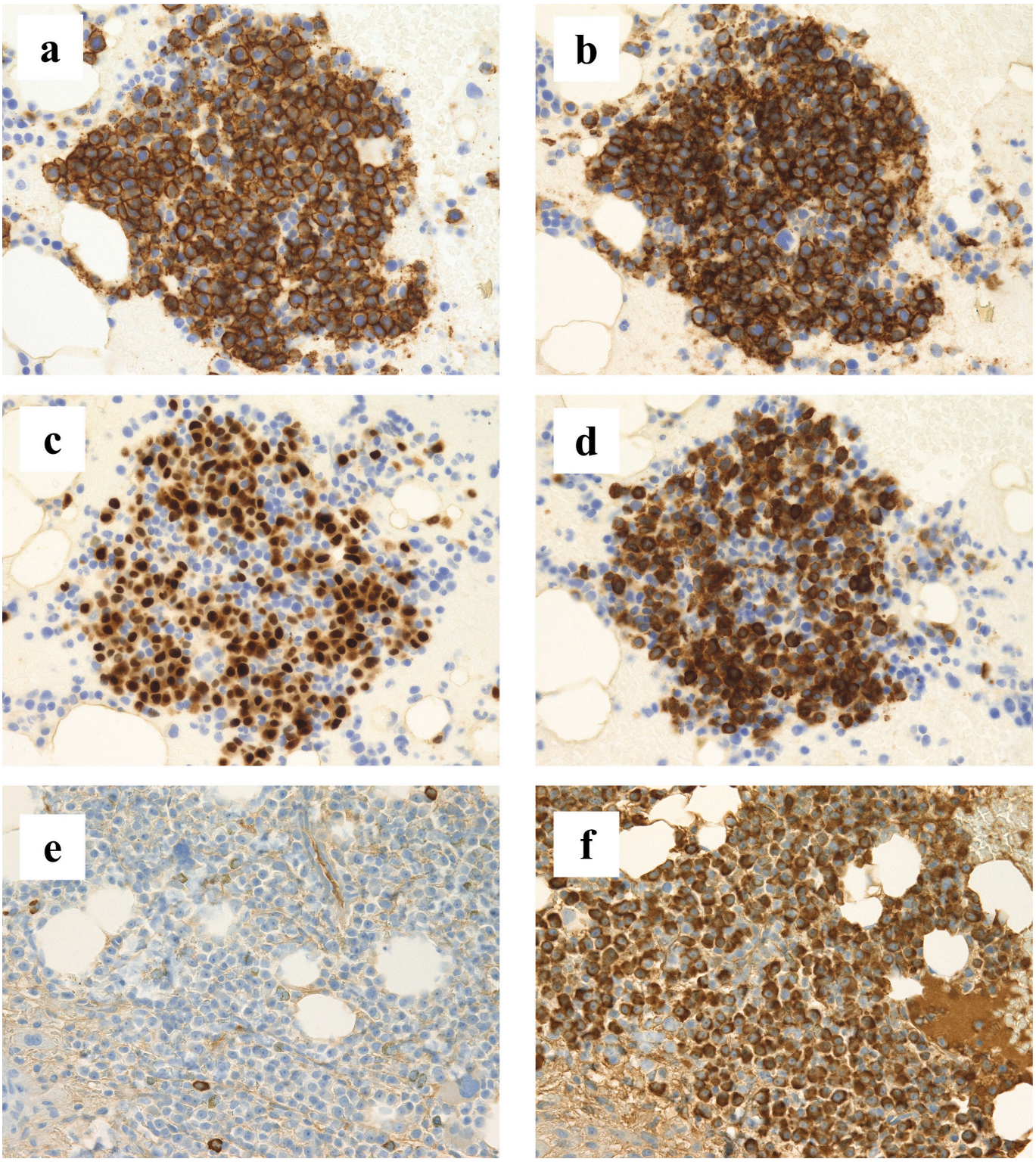

Fig. 1. Immunohistochemical staining patterns for PCM.
a: CD138 staining patterns. Expression was observed on the membranes of plasma cells. b: CD56 staining patterns. Expression is observed in 90 % of CD138-positive cells and is localized to the cell membrane of plasma cells. c: Cyclin D1 staining patterns. Expression is observed in 40 % of CD138-positive cells and is localized to the nuclei of plasma cells. d: CD79a staining pattern. Expression is observed in less than 80 % of the CD138-positive cells and is localized to the cytoplasm of plasma cells. e: Igκ staining pattern. Only a few plasma cells tested positive. f: Igλ staining pattern. Compared to Igκ, there is a 10-fold or more difference in expression, indicating light chain restriction.

Table 1
Immunohistochemical staining for PCM.

Antibody	Result	Number of cases (%)
CD138	Positive	115/116 (99.1)
	Negative	1/116 (0.9)
CD56	Positive	85/116 (73.3)
	Negative	31/116 (26.7)
CD79a	Positive	70/116 (60.3)
	Downregulation	46/116 (39.7)
cyclin D1	Positive	42/116 (36.2)
	Negative	74/116 (63.8)
light chain restriction	Positive	105/116 (90.5)
	Negative	0/116 (0)
	U.D.	11/116 (9.5)

U.D.: undetermined. PCM: Plasma cell myeloma.
All cases evaluated as U.D. were based on immunohistochemical staining.

Table 2
Details of PCM cases with light chain restriction undetermined.

No.	CD79a	CD56	cyclinD1
1	Positive	Positive	Negative
2	Positive	Positive	Negative
3	Positive	Positive	Negative
4	Positive	Positive	Negative
5	Positive	Positive	Negative
6	Downregulation	Negative	Negative
7	Positive	Positive	Positive
8	Downregulation	Negative	Negative
9	Downregulation	Positive	Positive
10	Downregulation	Negative	Positive
11	Positive	Positive	Negative

Table 3
Comparison of CD56 expression and clinical information.

		CD56-positive	CD56-negative	*p-value*
Sex, $N = 116$	male: n (%) female: n (%)	55 (47.4) 30 (25.9)	17 (14.6) 14 (12.1)	0.389
Age: median (range), $N = 116$		69 (39–88)	69 (30–87)	0.565
Ca, mg/dL: median (range), $N = 96$		9.2 (6.6–11.8)	9.3 (8.2–11.3)	0.329
Alb, g/L: median (range), $N = 94$		3.6 (1.2–5.1)	3.6 (2.3–4.9)	0.390
Cre, mg/dL: median (range), $N = 94$		0.9 (0.5–11.5)	0.8 (0.5–7.7)	0.239
Hb, g/dL: median (range), $N = 97$		11.7 (6.2–17.1)	11.9 (6.5–15.5)	0.348
Bone disorder, $N = 67$	+: n (%) -: n (%)	29 (43.3) 21 (31.3)	12 (17.9) 5 (7.5)	0.357
Serum light chain, $N = 35$	+: n (%) -: n (%)	23 (65.7) 3 (8.6)	6 (17.1) 3 (8.6)	0.161
Urine B-J protein, $N = 68$	+: n (%) -: n (%)	44 (64.7) 11 (16.2)	8 (11.8) 5 (7.3)	0.158
Serum IgG, mg/dL: median (range), $N = 89$		3762 (3132–8550)	4868 (3242–9982)	0.282
Serum IgA, mg/dL: median (range), $N = 88$		3813 (2679–5609)	3026 (2593–3459)	0.222
Serum β2-microglobulin, mg/L: median (range), $N = 66$		3.5 (1.6–52.0)	3.8 (1.8–14.5)	0.114

Independent-test. Ca: calcium, Alb: albumin, Cre: creatinine, Hb: hemoglobin, B-J: Bence Jones.

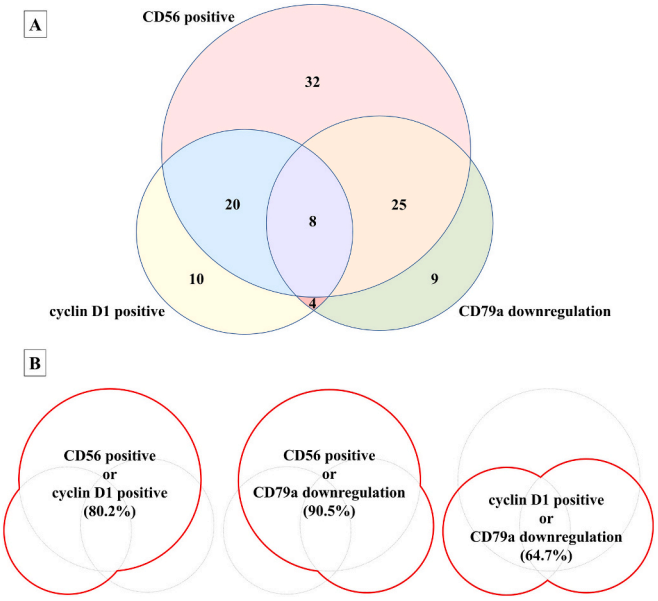

Fig. 2. Comparison of PCM detection rates with CD56, CD79a, and cyclin D1.
A: Number of detected cases of the three antibodies in 116 PCM cases. CD56-positive cells were observed in 85 cases (73.3 %), CD79a was downregulated in 46 cases (39.7 %), and cyclin D1 was positive in 42 cases (36.2 %). B: PCM detection rate for the two-antibody combination pattern. CD56 or cyclin D1-positive in 93 cases (80.2 %), CD56-positive or CD79a downregulation in 105 cases (90.5 %), and cyclin D1-positive or reduced CD79a expression in 75 cases (64.7 %). CD56-positive cells, reduced CD79a expression, or cyclin D1-positive cells were observed in 108 cases (93.1 %).

3.4. Evaluation of CD56 expression in LPL and MZL

For the differential diagnosis of PCM, the expression of CD56, CD79a, and cyclin D1 was evaluated in the LPL and MZL. CD79a expression was downregulated in two of the eight MZL cases (25.0 %), whereas CD56 and cyclin D1 expression were not detected in either LPL or MZL (Table 4). Therefore, CD56 and cyclin D1 show 100 % specificity for PCM. The sensitivities for differentiating PCM from LPL and MZL were 73.3 % CD56, 61.3 % for CD79a, and 36.2 % for cyclin D1.

4. Discussion

In this study, we evaluated the diagnostic utility of CD56 in bone marrow PCM specimens by immunohistochemical staining. The diagnostic rate of PCM was also examined when CD56 was combined with the established markers CD79a and cyclin D1. This study showed that CD56 had the highest expression frequency (73.3 %) and suggested that the diagnostic utility was improved when CD56 was used in combination with CD79a or cyclin D1, rather than alone. Additionally, immunohistochemical analyses of CD56, CD79a, and cyclin D1 were performed to aid in the diagnosis of LPL and MZL, which are difficult to distinguish from PCM. Although the number of cases varied because the

Table 4
Comparison of immunohistochemical staining for LPL and MZL.

Antibody	Result	LPL (%)	MZL (%)
CD56	Positive	0/7 (0)	0/8 (0)
	Negative	7/7 (100)	8/8 (100)
CD79a	Positive	7/7 (100)	6/8 (75)
	Downregulation	0/7 (0)	2/8 (25)
Cyclin D1	Positive	0/7 (0)	0/8 (0)
	Negative	7/7 (100)	8/8 (100)

LPL: Lymphoplasmacytic lymphoma, MZL: Marginal zone lymphoma.

analysis was limited to bone marrow specimens, CD56 and cyclin D1 were not expressed in LPL or MZL, resulting in a specificity of 100 % for distinguishing PCM. The specificity of CD79a was 61.3 %, which was slightly lower than that of the other two antibodies. Thus, CD56 was found to have the highest sensitivity and specificity for PCM compared to CD79a and cyclin D1. Furthermore, the use of CD79a and cyclin D1 as supplementary markers along with CD56 may enhance the diagnostic accuracy of PCM. As treatment strategies for PCM and lymphomas differ significantly [5,13-16], differential diagnosis is crucial.

Although PCM diagnosis is not difficult when light chain restriction is clear, this restriction is often not distinctly evident. Notably, detection of light chain restriction by immunostaining frequently becomes undeterminable, affecting the diagnosis of PCM. While ISH can remove this instability, its high cost and lack of insurance coverage impose a significant financial burden on clinical laboratories. In some cases, flow cytometry can identify light chain restrictions, eliminating the need for expensive ISH methods. For these reasons, the examination of light chain restriction in pathological testing is primarily based on immunostaining. Therefore, most of the light chain restrictions examined in this study were also investigated by immunostaining, with only a few cases using ISH. In the diagnosis of PCM, the detection of tumor cells by antibodies other than Igκ and Igλ is crucial. Tanaka et al. reported that downregulation of CD79a and overexpression of cyclin D1 served as strong diagnostic clues, regardless of light-chain restriction results. However, the combination of CD79a and cyclin D1 alone could only diagnose 59 % of the PCM cases [3]. Van Camp et al. [11] and Ely et al. [7] reported that CD56 is positive in approximately 70 % of PCM cases. In this study, the expression of the three antibodies was mutually exclusive. These antibodies are expected to improve the detection rate of PCM. As noted by Tanaka et al. [3], a significant advantage of this three-marker combination is that the three monoclonal antibodies are widely used in many laboratories.

Among the 116 PCM cases included in this study, one was negative for CD138. Clusters of uniformly sized plasma cell–like cells with perinuclear clearance are observed in the bone marrow. Tumor cells were negative for CD56, positive for CD79a, and expressed cyclin D1 in 50 % of cases. Although differentiation from mantle cell lymphoma was initially considered, a final diagnosis of PCM was made based on clinical presentation and flow cytometry findings. In such cases, the loss of CD138 expression in the PCM may reflect incomplete maturation of B cells following class switching before full differentiation into plasma cells [17-20]. Because only one case of CD138-negative PCM was identified in this study, the diagnostic utility of CD56 in such cases remains unclear and warrants further investigation.

CD56 is a member of the immunoglobulin superfamily and functions as a membrane glycoprotein involved in cell adhesion, growth, and migration [21]. In PCM, CD56 mediates homotypic adhesion between neoplastic plasma cells and osteoclasts within the bone marrow, resulting in cellular clustering [7]. The expression of CD56 in PCM may restrict tumor cell mobility and promote retention within the bone marrow [21]. Conversely, in cases of CD56-negative PCM, the absence of CD56 may enhance the influence of matrix metalloproteinase-9 (MMP-9) within the marrow environment, thereby facilitating tumor cell invasion and metastasis [18,21]. Clinically, CD56-positive PCM is more frequently associated with Stage I or II disease, whereas CD56-negative PCM tends to be present in Stage III and is considered more aggressive [22]. Therefore, the assessment of CD56 expression is valuable not only for pathological diagnosis but also as a prognostic indicator for patients with PCM.

In this study, no correlation was found between CD56 expression and clinical manifestations such as CRAB or associated laboratory abnormalities. Although the mechanisms underlying CD56 expression in PCM remain unclear, previous studies indicate that it is strongly associated with osteolytic lesions. Ely et al. reported that CD56 expression was significantly higher in patients with PCM with osteolytic lesions than in those without lesions [7]. However, in the present study, no significant association was observed between CD56 expression and the presence or absence of osteolytic lesions ($p = 0.357$). The discrepancies between our findings and those previously reported may be attributed to differences in the number of cases analyzed and the different biopsy approaches used. The study by Ely et al. included 352 osteolytic lesions; however, we examined 116 specimens at diagnosis, suggesting that differences in clinical staging may have contributed to these findings.

Previous studies have reported associations between CD56 expression and not only bone lesions, but also other clinical features and prognoses [18]. Patients with CD56-positive PCM showed improved treatment efficacy when CREB1/RSK2 inhibitors and lenalidomide were used [5]. Patients with CD56-negative PCM have significantly poorer prognoses than those with CD56-positive PCM, with a higher incidence of renal impairment, presence of Bence-Jones protein, and extramedullary disease [18,21]. Furthermore, the International Staging System (ISS) for multiple myeloma proposes a staging system based on two laboratory values: serum albumin and serum β2-microglobulin [23,24]. In the present study, the latter tended to be higher in CD56-positive cases; however, the difference was not statistically significant. This may partly result from the limited number of cases for which β2-microglobulin levels were available (66/116 cases).

Based on the findings of this study, in cases where a plasma cell-like morphology was observed, the presence of CD138 and CD56 expression strongly suggested a diagnosis of PCM. Even in the absence of CD56 expression, PCM should be strongly suspected if decreased CD79a or cyclin D1 expression is observed. Conversely, in cases lacking CD56 expression and showing neither decreased CD79a nor cyclin D1 expression, the likelihood of PCM is low, and alternative differential diagnoses should be considered (Fig. 3).

In the present study, we evaluated the diagnostic utility and clinical relevance of CD56 in the pathological evaluation of PCM. Among existing PCM markers, CD56 showed the highest frequency of expression in PCM. The combination of CD56 with CD79a and cyclin D1 improved the diagnostic accuracy and proved useful in distinguishing PCM from LPL and MZL. These findings underscore the value of CD56 as a novel marker for the differential diagnosis of PCM and highlight the need for further research to support its future clinical application.

5. Conclusions

Among the existing PCM markers, CD56 showed the highest expression frequency. Furthermore, the combination of CD56, CD79a, and cyclin D1 can further improve the diagnostic accuracy of PCM, and

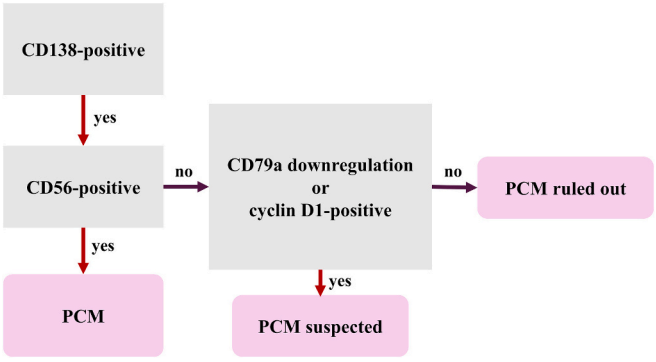

Fig. 3. Algorithm for PCM diagnosis using immunohistochemical staining. With the presence of plasmacytoid cells by H&E staining, the expression of CD138 should be initially examined. The expression of CD56 and CD138 is strongly suggestive of PCM (Plasma cell myeloma). In cases in which CD56 is negative, PCM should be suspected if downregulation of CD79a or cyclin D1 is observed. In contrast, in cases negative for CD56, CD79a, and cyclin D1, PCM is unlikely, and differential diagnoses, including MZL and LPL, should be considered.

we expect these markers to be actively utilized.

CRediT authorship contribution statement

Midori Imai: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Asami Nishikori:** Writing – review & editing, Supervision. **Tomoka Haratake:** Investigation, Data curation. **Midori Filiz Nishimura:** Writing – review & editing, Supervision. **Rio Yamada:** Investigation. **Syoma Kato:** Investigation, Data curation. **Mizuha Tabe:** Investigation, Data curation. **Hiroyuki Yanai:** Investigation. **Hidetaka Yamamoto:** Investigation. **Yasuharu Sato:** Writing – review & editing, Supervision, Conceptualization.

Consent for publication

Not applicable.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Okayama University (protocol numbers 2204–003 and 2102–002) and was performed in accordance with the tenets of the Declaration of Helsinki. Given that the study was retrospective and used residual diagnostic samples, the requirement for written informed consent was waived. Instead, information about the study was disclosed to potential participants, and they were given the opportunity to opt out, in accordance with the committee's approval.

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Declaration of competing interest

The authors declare no competing interests.

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Data availability

The datasets used and/or analyzed in the current study are available from the corresponding author upon reasonable request.

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