Plasmacytoma in patients with multiple myeloma: morphology and immunohistochemistry

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Abstract

Background. To study the histological structure and immunohistochemical (IHC) parameters of the plasmacytoma tumor substrate in patients with MM. **Methods.** The study included 21 patients (10 men/11 women) aged 23 to 73 years old with a newly diagnosed MM complicated by plasmacytoma. Bone plasmacytoma was diagnosed in 14 patients, and extramedullary plasmacytoma was diagnosed in 7 patients. Plasmacytoma tissue specimens were examined using a LEICA DM4000B microscope. Anti-CD56, CD166, CXCR4, Ki-67, c-MYC antibody panels were used for the IHC study of plasmacytoma biopsy. **Results.** When comparing the morphology of bone and extramedullary plasmacytoma, no significant differences were revealed, however, when the substrate of the extramedullary plasmacytoma was compared to the bone plasmacytoma substrate it was more often represented by tumor cells with immature morphology (57.1% vs. 28.6%). We founded a significant difference in the expression of CD166 in bone and extramedullary plasmacytoma. It was shown that the mean values of the CD166 expression in bone plasmacytoma cells were significantly higher ($p = 0.033$) and amounted to $36.29 \pm 7.61\%$ versus $9.57 \pm 8.46\%$ in extramedullary plasmacytoma cells. We noticed that in the cells of the extramedullary plasmacytoma, there were higher values in the Ki-67 index than observed in comparison to the cells of the bone plasmacytoma independent of the cells' morphology. **Conclusion.** The mechanisms involved in the dissemination of tumor plasma cells are currently unexplored. Our study revealed significant differences in the IHC parameters of the tumor substrate from extramedullary and bone plasmacytoma. Thus, the expression of the CD166 in extramedullary plasmacytoma cells is almost 4 times lower than that in bone plasmacytoma cells, which may indicate the involvement of CD166 in the mechanisms of bone destruction. A high proliferative activity of extramedullary plasmacytoma cells was shown when compared to bone plasmacytoma cells.

Introduction

The introduction of highly sensitive imaging methods into clinical practice facilitates the more frequent detection of bone and extramedullary plasmacytoma in patients with MM. In case of intraosseous tumor growth, the destruction of the cortical bone occurs and plasmacytoma extends beyond the bone borders, invading the surrounding tissues or spinal canal. In case of hematogenous dissemination of plasma cells, isolated extramedullary plasmacytoma is formed in various organs and tissues, without anatomical association with bone. Invasive surgical procedures can lead to the local plasmacytoma formation - in the area of manipulation.¹⁻³ According to the results of clinical studies, it was revealed that in patients with newly diagnosed MM the occurrence of plasmacytoma varies from 3.5% to 18%, and in patients with relapse of the disease it varies from 6% to 30%.^{1,3-8} The variability of these values is due to the lack of clear terminology-defining criteria. Thus, some authors under the concept of 'extramedullary lesion' understand both bone plasmacytoma and extramedullary plasmacytoma, while other researchers exclude bone plasmacytoma from the spectrum of extramedullary myeloma.^{1,3,5,6} If we within the term "extramedullary lesion" consider only haematogenously-formed plasmacytomas not related to bone, the frequency of detection of such in the newly diagnosed MM will not exceed 3.5-6%. In the published

papers, insufficient attention has been paid to the study of plasmacytoma tumor substrate morphological structure in patients with MM. In a small series of observations, it was shown that cells of bone plasmacytoma are characterized by mature morphology, and the substrate of extramedullary plasmacytoma is more often represented by cells with immature morphology.^{3,9-12}

The reasons why myeloma cells "escape" from bone marrow stromal microenvironment control, yielding the formation of bone and extramedullary plasmacytoma, are being actively studied. The pathogenesis of extramedullary tumor growth is complex, it has not been studied in detail, and is probably due to the loss of the interaction between plasma cells and the bone marrow microenvironment, which plays a crucial role in the processes of cell proliferation and migration. Among the causes of extramedullary plasma cell relocation, downregulation of adhesion molecules expression (CD56, VLA-4), dysregulation of chemokine receptors (CCR1, CCR2, CXCR4), and an increase in heparanase-1 activity, are suggested.^{1,3} These mechanisms are currently only suggested, since there are no scientific studies on a large number of patients, and the results of studies in small patient populations presented in the literature are contradictory.

Thus, it is important to assess the morphological patterns of bone plasmacytoma and extramedullary plasmacytoma biopsies, as well as to analyze the expression of a series of markers that may presumably participate in the pathogenesis of myeloma cells spreading beyond the bone marrow.

Background of the work was to study the histological structure and IHC parameters of the plasmacytoma tumor substrate in patients with MM.

Methods

The study included 21 patients (10 men and 11 women) aged 23 to 73 years old with a newly diagnosed MM complicated by plasmacytoma. Patients with solitary plasmacytomas were excluded. Bone plasmacytoma was diagnosed in 14 patients, and extramedullary plasmacytoma was diagnosed in 7 patients. Bone plasmacytoma was more often revealed in flat bones - vertebrae, ribs, skull bones. Isolated cases of clavicle or humerus lesions were registered. Extramedullary plasmacytoma was found in various organs and tissues: liver, stomach, abdominal cavity and retroperitoneal space, in the soft tissues of the neck, breast, muscles of the shoulder girdle, and skin.

MM diagnosis was verified in accordance with the criteria developed by the International Multiple Myeloma Working Group 2014. Diagnostic methods included bone marrow cytological examination, immunochemical blood and urine examination, x-ray examination of the skeletal bones, and also clinical blood analysis and blood chemistry. The follow-up period ranged from 5 to 62 months (median 24 months).

In all patients, plasmacytoma biopsy samples were collected after written informed consent was given by each person, according to the local ethical committees and the Helsinki Declaration protocol. This study

was approved by the Local Ethical committee of FSFI «National Research Center for Hematology» of the Ministry of Healthcare of the Russian Federation.

A plasmacytoma biopsy was performed in all patients prior to treatment start. The plasmacytoma tissue specimens were examined using a LEICA DM4000B microscope. Anti-CD56, CD166, CXCR4, Ki-67, c-MYC antibody panel was used for the IHC study of plasmacytoma biopsy. 10 fields of view were viewed at a 400-fold magnification to determine the protein expression. The evaluation of the marker's expression was carried out using a semi-quantitative method. The percentage of cells expressing the protein was calculated relative to the total number of cells in the tumor substrate. Where staining with antibodies was achieved, the following values of expression were considered positive: $\geq 10\%$ for CD56, $\geq 50\%$ for CD166, $\geq 20\%$ for CXCR4, $\geq 40\%$ for c-MYC¹³⁻¹⁷ The level of proliferative activity was expressed as a percentage and assessed based on the expression of Ki-67 marker by tumor cells.

Frequency analysis (cross tables, a Fisher-Freeman test) was used for statistical analysis. A Student's t-test was used to assess the significance of the differences in two independent samples. The critical level of significance 'p' was set as 0.05. Calculations were carried out using the SPSS 16.0.2 statistical software.

Results

Histological examination of plasmacytoma in MM patients.

Depending on the cell composition, 2 morphological variants were distinguished in the plasmacytoma biopsy specimens:

Variant I: massive infiltration by mature plasma cells;

Variant II: massive infiltration by plasma cells with immature morphology (more than 50% tumor cells of specimens were proplasmocytes, more than 5% of the tumor cells were plasmoblasts).

Figures 1-4 are present photographs of plasmacytoma tissue specimens illustrating various tumor substrate morphological variants.

Table 1 presents the occurrence of various morphological variants in the tumor substrate, identified in the plasmacytoma biopsy material taken from MM patients. Biopsy microscopic examination of bone plasmacytoma from 10 patients revealed massive infiltration by mature plasma cells, and in 4 patients there was a massive infiltration by tumor cells with immature morphology. Microscopic examination of extramedullary plasmacytoma biopsies revealed massive infiltration by mature plasma cells in 3 patients. In 4 cases, the tumor substrate of the plasmacytoma was represented by tumor cells with immature morphology.

When comparing morphological patterns of bone and extramedullary plasmacytoma, no significant differences were revealed, however, the substrate of the extramedullary plasmacytoma was more often

represented by tumor cells with immature morphology when compared to the bone plasmacytoma (57.1% vs. 28.6%).

Immunohistochemical study of plasmacytoma in MM patients.

We carried out a comparative analysis of the quantitative parameters of the studied markers expression in the biopsy specimens of bone and extramedullary plasmacytomas. Table 2 presents the average values of the marker's expression.

When analyzing the results obtained, a significant difference was found in terms of the cell adhesion molecule CD166 and Ki-67 protein. Where, the mean values of CD166 molecule expression in cells of the bone plasmacytoma were significantly higher ($p = 0.044$) and amounted to $36.29 \pm 7.61\%$ versus $9.57 \pm 8.46\%$ in the cells of the extramedullary plasmacytoma, it was also demonstrated that the mean Ki-67 values in cells of the extramedullary plasmacytoma were significantly higher ($p = 0.004$) and amounted to $61.43 \pm 10.50\%$ versus $25.36 \pm 5.63\%$ in the bone plasmacytoma cells. Figures 5-10 present images of IHC plasmacytoma specimens from MM patients.

Correlation of the marker's expression in plasmacytoma cells with the morphological picture of the plasmacytoma substrate.

We have analyzed plasmacytoma cells expression in the studied markers depending on plasmacytoma cells morphological structure. In 13 patients the plasmacytoma tumor substrate was represented by mature plasma cells. In 8 patients, the cells were in the immature morphology. Table 3 shows the mean average values of the marker's expression in the plasmacytomas with the mature and immature cell morphology.

When analyzing the results obtained, a statistically significant difference was revealed only for the cell adhesion molecule CD166. Where, the average values of CD166 expression in cells with mature morphology were significantly higher than in cells with immature morphology ($p = 0.025$), and amounted to $38.23 \pm 8.37\%$ versus $9.75 \pm 5.87\%$.

The pathobiological basis of the higher rates of the CD166 expression in mature plasmacytoma plasma cells, in contrast to immature cells, is currently not fully understood and requires further study.

Discussion

There have only been a few studies conducted investigating the morphological picture of plasmacytoma biopsies. Some studies have shown that cells in the bone plasmacytoma are more often characterized by a mature morphology, while cells in the extramedullary plasmacytoma are represented by young, immature cell types.⁹⁻¹¹ It should be noted that most of these works are devoted to the study of the extramedullary MM relapses, and the morphological features of the tumor substrate cells in newly diagnosed MM and the relapse of the disease may differ.

We investigated the morphological features of the plasmacytoma substrate in 14 patients with bone plasmacytoma and 7 patients with extramedullary plasmacytoma in newly diagnosed MM patients. When comparing the morphological picture of the bone and the extramedullary plasmacytoma, no significant differences were revealed; however, the substrate of the extramedullary plasmacytoma compared to the bone plasmacytoma substrate was more often represented by tumor cells with an immature morphology (57.1% vs. 28.6%).

A possible mechanism for the tumor plasma cell expansion beyond the bone marrow is the downregulation of the adhesion molecules expression (for example, CD56), as a result of which the cell loses its connection with the stromal microenvironment.^{18,19} The role of the expression of another cell adhesion molecule, CD166, is now actively being investigated in MM. A study on mouse models has shown that CD166 blocks osteoblastogenesis by inhibiting the RUNX2 expression, which is an important transcription factor influencing the differentiation of osteoblasts. In addition, CD166 activates osteoclastogenesis, shifting the balance between RANKL and osteoprotegerin. The CD166 blockage in mouse myeloma cells results in a longer survival, lower total tumor mass, and less pronounced osteolysis compared to individuals with CD166-positive cells.²⁰ Thus, it is assumed that CD166 is a predictor for lytic bone lesions, as it participates in osteogenesis modulation.

In our study, a statistically significant difference in the expression of CD166 was revealed after comparing the expression of this marker in cells of the bone and extramedullary plasmacytoma. It was shown that the mean values of the CD166 expression in the bone plasmacytoma cells were significantly higher ($p = 0.033$) and amounted to $36.29 \pm 7.61\%$ versus $9.57 \pm 8.46\%$ in the extramedullary plasmacytoma cells. This may indicate the involvement of CD166 in the mechanisms in bone destruction. In addition, it was demonstrated that the mean expression values of CD166 in plasmacytoma cells with a mature morphology were significantly higher ($p = 0.012$) and amounted to $38.23 \pm 8.37\%$ versus $9.75 \pm 5.87\%$ in the plasmacytoma cells with an immature morphology.

SDF-1 α and a chemokine receptor, CXCR4, are involved in the processes of cell homing and cell migration. It has been proven that myeloma cells can express these markers on their surface.^{21,22} Downregulation of the chemokine receptors is considered to be a possible mechanism leading to a weakening of the connection between the myeloma cells and the bone marrow stroma, thus promoting their dissemination. The absence of CXCR4 on the tumor plasma cell surface, while not being a strict predictive factor of extramedullary lesions, probably plays a role in the formation of extraosseous foci.

There have been only few studies on the role of chemokine receptors in the MM pathogenesis, and the data presented in the literature is contradictory. We have demonstrated a high frequency of CXCR4 expression in the plasmacytoma cells. These results are comparable with the data from a study by M. Weinstock et al., where 38.5% of patients showed CXCR4 expression in the tumor substrate.²³

According to the data presented in the literature, the proliferative activity of the tumor cells in MM is low. An increased Ki-67 index is a marker of active cell growth and correlates with the progression of the

disease. Researchers from the Mayo Clinic showed that a high level of proliferative activity, even with a minimum number of plasma cells in the bone marrow, is a risk factor for early relapse and high mortality.²⁴

We noticed that in the cells of extramedullary plasmacytoma, there were higher values of the Ki-67 index observed in comparison to cells in the bone plasmacytoma. This data is comparable with the results of a single-center study from Germany, which demonstrated a high proliferative activity in the extramedullary plasmacytoma biopsy specimens from 24 patients with extramedullary MM relapse.²⁵

Interestingly, our study shows that Ki67 is higher in extramedullary plasmacytomas, and that there is no difference in the mature or the immature morphology of a tumor. There has been an insufficient amount of studies devoted to the investigation of c-MYC in the tumor substrate of plasmacytoma. In the study by L. Billecke et al. it was noted that the overexpression of the c-MYC gene in the plasmacytoma substrate was seen in 18% of patients with bone plasmacytoma and in 28% of patients with extramedullary plasmacytoma.²⁶

Given the low frequency of extramedullary lesions in MM, as well as the fact that it is not always possible to perform a plasmacytoma biopsy due to its inaccessible localization, there have been no studies of the plasmacytoma substrates in large patient populations.

Conclusion

The mechanisms involved in the dissemination of tumor cells outside the bone marrow are currently unexplored. Our study, even on a small sample of patients, revealed significant differences in the IHC parameters of the tumor substrate from the extramedullary plasmacytoma and the bone plasmacytoma. Thus, the expression of a cell adhesion molecule, CD166, in the extramedullary plasmacytoma cells is almost 4 times lower than that in the bone plasmacytoma cells, which may indicate the involvement of CD166 in osteogenesis modulation. A high proliferative activity of extramedullary plasmacytoma cells was shown when compared to bone plasmacytoma cells.

A more thorough study of the tumor substrate in MM is likely to reveal some regular patterns in the formation of the extramedullary lesions, which will contribute to a better understanding of the tumor's biology.

Abbreviations

MM - multiple myeloma

IHC - Immunohistochemistry

Declarations

Ethics approval and consent to participate

This study was approved by the Local Ethical committee of FSFI «National Research Center for Hematology» of the Ministry of Healthcare of the Russian Federation.

Consent for publication

Not Applicable

Availability of data and material

Please contact the author Firsova Maiia (firs-maiia@yandex.ru) upon reasonable requests.

Competing interests

The authors report no conflicts of interest in this work.

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Authors' contributions

M.V. Firsova: concept, data collection, article writing;

L.P. Mendeleeva: concept and design, interpretation of data;

A.M. Kovrigina: performance of histological and immunohistochemistry study of bone marrow and plasmacytoma specimens, interpretation of data;

M.V. Soloviev: provision of materials, article writing;

V.G. Savchenko: concept, final approval of the article.

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Tables

Table 1. The frequency of various plasmacytoma morphological variants in MM patients.

Plasmacytoma localisation	Morphological plasmacytoma variant-massive infiltration by plasma cell with		p
	Mature morphology	Immature morphology	
Bone	71.4% (10/14)	28.6% (4/14)	0.35
Extramedullary	42.9% (3/7)	57.1% (4/7)	

Table 2. The parameters of marker's expression in bone and extramedullary plasmacytoma in MM patients.

Marker	MM patients with plasmacytoma	Expression parameters (%)		p
		$\bar{x}$	$\pm m$	
CD56	Bone (n=14)	54.29	10.18	0.165
	Extramedullary (n=7)	28.57	14.86	
CD166	Bone (n=14)	36.29	7.61	0.044
	Extramedullary (n=7)	9.57	8.46	
CXCR4	Bone (n=14)	45.50	9.35	0.413
	Extramedullary (n=7)	31.71	13.91	
Ki-67	Bone (n=14)	25.36	5.63	0.004
	Extramedullary (n=7)	61.43	10.50	
c-MYC	Bone (n=14)	33.29	8.37	0.748
	Extramedullary (n=7)	37.86	10.57	

Table 3. Parameters of the marker's expression in plasmacytoma specimens from patients with MM

Marker	Plasmacytoma cell morphology	Expression parameters(%)		p
		$\bar{x}$	$\pm m$	
CD56	Mature (n=13)	39.23	9.28	0.351
	Immature (n=8)	56.25	17.10	
CD166	Mature (n=13)	38.23	8.37	0.025
	Immature (n=8)	9.75	5.87	
CXCR4	Mature (n=13)	33.85	8.47	0.253
	Immature (n=8)	52.38	14.65	
Ki-67	Mature (n=13)	29.77	7.73	0.124
	Immature (n=8)	49.75	9.61	
c-MYC	Mature (n=13)	34.15	7.15	0.901
	Immature (n=8)	35.88	13.06	

Figures

Figure 1

The histology of stomach extramedullary plasmacytoma in MM patients. Hematoxylin + eosin staining. Massive infiltration by mature plasma cells, x200;

Figure 2

The histology of rib bone plasmacytoma in MM patients. Hematoxylin + eosin staining. Massive infiltration by mature plasma cells, x200;

Figure 3

The histology of skull bone plasmacytoma in MM patients. Hematoxylin + eosin staining. Massive infiltration by tumor cells with immature morphology (plasmablasts have the blast structure of the nucleus, large nucleoli, and narrow cytoplasm);. x400.

Figure 4

The histology of extramedullary plasmacytoma in the soft tissues of the neck in MM patients. Hematoxylin + eosin staining. Massive infiltration by tumor cells with immature morphology, x200.

Figure 5

Mammary gland extramedullary plasmacytoma. Staining using antibodies to CD56, enzyme immunoassay. Membrane expression more than 90% of the tumor cells. x200;

Figure 6

Mammary gland extramedullary plasmacytoma. Staining using antibodies to CD166, enzyme immunoassay. Cytoplasmic and membrane expression. Expression of CD166 in single cells. x200;

Figure 7

Skin extramedullary plasmacytoma. Staining using antibodies to CD166, enzyme immunoassay. Cytoplasmic and membrane expression in 30% of the tumor cells. x100;

Figure 8

Rib bone plasmacytoma. Staining using antibodies to Ki-67. Nuclear expression in 25% of the tumor cells.
x200;

Figure 9

Stomach extramedullary plasmacytoma. Staining using antibodies to Ki-67. Nuclear expression in 65% of the tumor cells. x200;

Figure 10

Stomach extramedullary plasmacytoma. Staining using antibodies to c-MYC. Nuclear expression in 15% of the tumor cells. x200