Plasma Cell Neoplasms Presenting with Masses: A Study on Morphology, Expression of CD56 and Cyclin D1, and Presence of Epstein-Barr Virus in 39 Thai Patients in Siriraj Hospital

Wiriya Pipatsakulroj MD*,
Kanapon Pradniwat MD*, Jitsupa Treetipsatit MD*

** Department of Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand*

Background: *Plasma cell neoplasms (PCNs) presenting with masses are not common. Variable morphology, expression of CD56 and cyclin D1, and Epstein-Barr virus (EBV)-encoded small RNA (EBER) status have been described with a promising diagnostic role. There is no data of these findings in Thai patients.*
Objective: *To study morphology, CD56 and cyclin D1 expression and EBER status in PCNs presenting with masses.*
Material and Method: *Thirty-nine mass-forming PCNs with available materials between 2006 and 2010 were identified from Siriraj Hospital pathology database. H&E slides were reviewed for morphologic grade according to Bartl grading system. Immunohistochemistry for CD56 and cyclin D1 and EBER in situ hybridization were analyzed on tissue microarray sections of the included cases.*
Results: *Of 39 cases, it comprised 31 (79.5%) plasma cell myelomas (PCMs), five (12.8%) osseous plasmacytomas (OPs), and three (7.7%) extramedullary plasmacytomas (EMPs). Intermediate-grade morphology was common to all types of PCNs. CD56 and cyclin D1 positivity were more often in PCMs comparing with OPs and EMPs; however, differences in expression of these markers among different types of PCNs were insignificant ($p>0.05$). An EBER-positive EMP was identified.*
Conclusion: *The majority of mass-forming plasma cell tumors in the studied population are PCM-related. Intermediate-grade morphology is common in all types of PCNs. A value of CD56 and cyclin D1 immunostains in discrimination between types of PCNs cannot be confirmed in the current study. Identification of the EBER-positive EMP suggests that EBV association in plasma cell tumor can be encountered in Thais.*

Keywords: *Plasma cell neoplasms, Plasmacytomas, CD56, Cyclin D1, EBER*

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Plasma cell neoplasms (PCNs) presenting with masses are not common. According to the literature, the incidence varies depending on tumor type, 7 to 18% for plasma cell myeloma (PCM)[1,2], 3 to 5% for osseous plasmacytoma (OP)[3], and 3 to 5% for extramedullary plasmacytoma (EMP)[3]. Distinction from B-cell lymphoma with plasmacytic differentiation as well as determination of the type of PCN (either primary plasmacytoma or myeloma-related tumor) is essential because of differences in treatment options and clinical outcomes. Although some morphologic features, CD56 or cyclin D1 expression and detection of Epstein-Barr virus (EBV) were claimed to be diagnostically helpful in distinction between PCM, plasmacytoma and B-cell lymphoma with plasmacytic differentiation[4-8], there are an increasing number of studies (especially those performed in Asian populations) that report different results. Therefore, additional studies in morphology, expression of these markers and EBV status in PCNs presenting with masses are needed to elucidate their diagnostic role. To our knowledge, there is no data in morphology, expression of CD56 and cyclin D1 and EBV status in Thai patients with PCNs presenting with masses.

The present study focused on morphology, CD56 and cyclin D1 expression, and EBV status in PCNs presenting with masses in Thai patients in Siriraj Hospital. Association of these parameters with tumor type, clinical data, and HIV status is also investigated.

Correspondence to:
Treetipsatit J, Department of Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Prannok Road, Bangkok Noi, Bangkok 10700, Thailand.
Phone: 0-2419-6520, Fax: 0-2411-4260
E-mail: jtreetipsatit@gmail.com

Material and Method

Case selection

A search of the Department of Pathology database at Siriraj Hospital to include the terms "plasma cell myeloma", "plasmacytoma", and "plasma cell neoplasm" that were diagnosed in any organs other than bone marrow between January 2006 and December 2010 yielded 39 cases with available material for study. Demographic data and clinical information including clinical staging, presence of bone marrow involvement, serum calcium level, serum creatinine level, hemoglobin level, presence of serum M-protein, and HIV status were recorded for each case. The authors used the criteria based on the 2008 WHO Classification of the Tumours of Haematopoietic and Lymphoid tissues[3], Guidelines for the diagnosis and management of multiple myeloma 2011[9] and Guidelines on the diagnosis and management of solitary plasmacytoma of bone, extramedullary plasmacytoma and multiple solitary plasmacytomas: 2009 update[10] to classify the tumors. A case that had M-protein in serum, bone marrow clonal plasma cells or plasmacytoma and/or related organ or tissue impairment (i.e. hypercalcemia (serum calcium level >2.75 mmol/l), renal insufficiency (serum creatinine level >173 μmol/l), anemia (hemoglobin level <10 g/dl), and abnormal results on skeletal survey) was classified as PCM. A case that presented with a solitary mass lesion without features of PCM was classified as either osseous plasmacytoma or extramedullary plasmacytoma according to the location of the tumor. The present study was approved by Siriraj Institutional Review Board (SIRB).

Histologic evaluation

The hematoxylin and eosin (H&E)-stained slides of the included cases were reviewed and classified according to Bartl grading system[11] by two authors (Treetipsatit J and Pipatsakulroj W) under a two-headed microscope.

Tissue microarray

The tissue microarray (TMA) of the included cases (either biopsy or excision specimen) were manually constructed by taking small core tissue samples, measuring 5 mm in diameter and 3 to 4 mm in height each, from a representative area in the donor block and placing them to recipient paraffin blocks. The samples were taken by a steel tube that was punched into the paraffin block and a solid steel stylet was inserted into the tube to transfer the sample into the recipient block. Since the majority of the cases demonstrated homogeneous morphology, one representative core tissue sample was taken from each case. The recipient paraffin block was sectioned at 4 μm for conventional H&E stain, immunohistochemistry and in situ hybridization analysis for EBV-encoded small RNA (EBER).

Immunohistochemistry

Immunohistochemical staining for CD56 (123C3.D5; Ready to use; Cell Marque) and cyclin D1 (SP4; 1:100; Thermo) was performed on the 4 μm-thick TMA sections using an automated immunostainer (BenchMark XT; Ventana, Tucson, AZ) with a polymer-based detection system (DakoEnVision System; Dakocytomation). Immunohistochemical evaluation was performed by two authors (Treetipsatit J and Pipatsakulroj W) under a two-headed microscope. A cut-off of 10% was adopted for all the markers used.

In situ hybridization

In situ hybridization analysis for EBER was performed on the TMA sections using a Ventana Kit according to the manufacturer's instruction with appropriate positive and negative controls.

Statistics

Results were analyzed in terms of frequency, percentage, mean, median, and range. Comparison between groups was evaluated by Fisher's exact test using the Statistic Package for the Social Sciences for Windows version 15.0 (SPSS Inc., Chicago, IL, USA). A p-value of 0.05 was considered significant.

Results

Clinical characteristics

Of 39 cases, it comprised 27 (69.23%) newly diagnosed PCMs, four (10.27%) relapsed PCMs, five (12.8%) OPs, and three (7.7%) EMPs. A summary of clinical information of each group is shown in Table 1.

For bone-related tumors, PCM comprised the majority of cases (22/27 cases; 81.48%); most were the HIV-negative, newly diagnosed patients. Axial bones were the most common site of involvement in both PCMs and OPs. There was no difference in mean age between PCMs with bone-related masses (mean 56.82; median 57) and OPs (mean 49.6; median 53) (p = 0.184, Fisher's exact test). Among PCMs with bone-related tumors, accompanying renal insufficiency, anemia, and abnormal result on skeletal survey were

found in 13.64%, 45.45%, and 50% of cases, respectively. None of these cases presented with hypercalcemia. An average extent of bone marrow involvement in PCM patients with bone-related tumors was 43.95%.

Of 12 extramedullary tumors, 75% were PCMs with extramedullary involvement. Almost half (44.44%) of these cases were newly diagnosed PCMs with Durie-Salmon stage I or II disease; only two cases were relapsed PCMs. Sites of the tumors varied and included unusual sites that have not been reported in the English literature such as parietal lobe of brain, pituitary gland, and pleura. Mean and median age of these patients was 56.22 and 53 years. Considering the accompanying clinical manifestations, the authors found that all of the PCMs with extramedullary involvement demonstrated serum M-protein while other signs of related organ/tissue impairment were found only in subsets of the cases [abnormal skeletal survey 4/9 (44.44%), anemia 3/9 (33.33%), hypercalcemia 1/9 (11.11%), and renal insufficiency 1/9 (11.11%)]. An average extent of bone marrow involvement in PCMs with extramedullary tumors was 41.44%. For three EMP cases in the current study, sites of the tumor seemed to confine to the head and neck region. There was no difference in mean age between patients with extramedullary PCMs and EMPs ($p = 0.495$, Fisher's exact test).

Table 1. Demographic data and clinical information

Clinical data	No. of cases	Percentage
Plasma cell myeloma (total 31 cases)		
Sex		
Male	21	67.70
Female	10	32.30
Age (years)		
Range	33-75	
Mean	56.65	
Median	55	
HIV status (21 cases available)		
HIV+	3	14.29
HIV-	18	85.71
Sites		
Bone-related	22	71
Extramedullary	9	29
Durie & Salmon stage		
Stage I	3	9.68
Stage II	9	29.03
Stage III	19	61.29
Osseous plasmacytoma (total 5 cases)		
Sex		
Male	5	100
Female	0	0
Age (years)		
Range	27-63	
Mean	49.60	
Median	53	
HIV status (2 cases available)		
HIV+	2	100
HIV-	0	0
Extramedullary plasmacytoma (total 3 cases)		
Sex		
Male	3	100
Female	0	0
Age (years)		
Range	35-61	
Mean	51.33	
Median	58	
HIV status (3 cases available)		
HIV+	3	100
HIV-	0	0

Of 26 cases with known HIV status, eight (30.8%) cases are HIV-positive comprising three EMPs, two PCMs with bone-related tumors, one PCM with extramedullary involvement, and two OPs. Of note, the authors found that primary plasmacytoma seemed to be found more often in HIV-positive patients ($p<0.001$, Fisher's exact test). Mean and median age of the HIV-positive cases were 51 and 58 years; no significant different was noted comparing to the HIV-negative cases ($p = 0.172$, Fisher's exact test). There was no relation between tumor site and HIV status.

Morphological findings

Morphological and immunohistochemical findings are summarized in Table 2. According to histological grading criteria described by Bartl et al[11], 14 of 39 cases (35.9%) were classified as low grade (Fig. 1a-b) and 25 cases (64.1%) as intermediate grade (Fig. 1c-e). Among the cases classified as low grade, those with small cell feature (Fig. 1a) and Marschalko feature (Fig. 1b) were 3/14 (21.43%) and 11/14 (78.57%) cases, respectively. Of 25 intermediate-grade cases, polymorphous feature (Fig. 1c) was most commonly found (11 cases; 44%), followed by asynchronous feature (Fig. 1d) (9 cases; 36%) and cleaved feature (Fig. 1e) (5 cases; 20%). Interestingly, the authors identified an OP with intermediate-grade morphology (polymorphous feature) and additionally showing intracytoplasmic vacuoles mimicking adenocarcinoma with signet ring cell feature (Fig 1f). None was classified as high grade/plasmablastic.

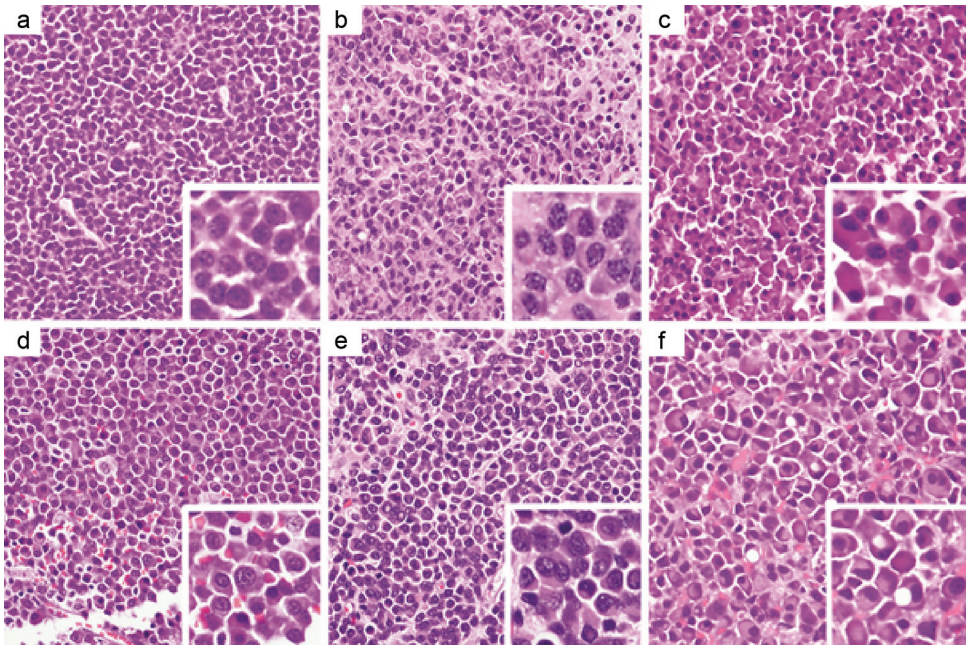

Fig. 1 Morphologic findings of plasma cell neoplasms presenting with masses [H&E x400 and x600 (inset)]. (a) Low grade with small cell feature showing neoplastic plasma cells with round lymphocytic nuclei and narrow rim of basophilic cytoplasms. (b) Low grade with Marschalko feature showing neoplastic plasma cells with eccentric cartwheel nuclei, perinuclear hofs and basophilic cytoplasms. (c) Intermediate grade with polymorphous feature. Note cellular and nuclear pleomorphism with some neoplastic plasma cells showing prominent central nucleoli. (d) Intermediate grade with asynchronous feature. Marked nuclear and cytoplasmic maturation asynchrony was observed with more than 50% of the neoplastic cells having large eccentric nuclei with prominent nucleoli, abundant basophilic cytoplasms and pronounced perinuclear hofs. (e) Intermediate grade with cleaved feature. The neoplastic plasma cells demonstrated notched, cleaved nuclei of variable size. (f) Neoplastic plasma cells of intermediate grade with intracytoplasmic vacuoles mimicking signet ring cells of adenocarcinoma.

In PCMs, intermediate-grade morphology was slightly more common than low grade. All the relapsed cases had intermediate-grade morphology. Comparing to the cases with bone-related tumors, percentage of cases with intermediate-grade morphology was higher in those with extramedullary involvement (83% vs. 54.55%). However, the difference was insignificant ($p = 0.228$, Fisher's exact test). Although all HIV-positive PCMs were classified as intermediate grade, the authors could not find significant difference in morphology between PCMs with different HIV status ($p = 0.186$, Fisher's exact test). Similar to PCMs, intermediate-grade morphology was more common in primary plasmacytomas.

Immunohistochemistry

Only 38 cases were available for CD56 and cyclin D1 immunohistochemical study. CD56 was positive in 15 of 38 cases: 11 PCMs with bone-related tumors, three PCMs with extramedullary involvement, and one OP. The majority of CD56-positive cases showed diffuse staining pattern (Fig. 2). There was no significant difference in CD56 positivity between each group of tumors ($p = 0.183$, Fisher's exact test).

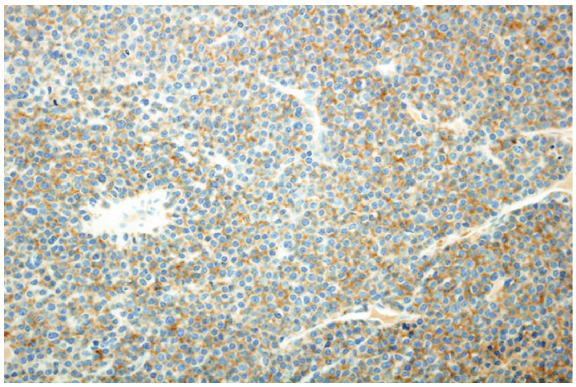

Fig. 2 Immunohistochemical staining pattern of CD56 in neoplastic plasma cells.

Table 2. Morphological grading and immunohistochemical findings

	No. of cases	Percentage
Plasma cell myeloma (total 31 cases)		
Bartl grade		
Low	12	38.7
Intermediate	19	61.3
High/plasmablastic	0	0
CD56 (30 cases available)		
Positive	14	46.7
Negative	16	53.3
Cyclin D1		
Positive	17	56.7
Negative	13	43.3
Osseous plasmacytoma (total 5 cases)		
Bartl grade		
Low	2	40
Intermediate	3	60
High/plasmablastic	0	0
CD56		
Positive	1	20
Negative	4	80
Cyclin D1		
Positive	1	20
Negative	4	80
Extramedullary plasmacytoma (total 3 cases)		
Bartl grade		
Low	0	0
Intermediate	3	100
High/plasmablastic	0	0
CD56		
Positive	0	0
Negative	3	100
Cyclin D1		
Positive	2	66.7
Negative	1	33.3

Cyclin D1 expression was observed in 20 of 38 cases: 13 PCMs with bone-related tumors, four PCMs with extramedullary involvement, two EMPs, and one OP. Two distinct staining patterns of cyclin D1, diffuse nuclear and cytoplasmic and patchy nuclear stainings, were observed (Fig. 3a-b). No association between the cyclin D1 staining pattern and type of the tumor was identified.

In bone-related tumors, PCMs with bone-related tumors seemed to express CD56 and cyclin D1 more frequent than OPs but the difference did not reach statistical significance (p>0.05, Fisher's exact test). Although, among the extramedullary tumors, only PCMs expressed CD56, the significance of staining difference between PCMs with extramedullary involvement and ECMs could not be concluded due to small numbers of EMP cases in the current study. HIV status did not affect CD56 and cyclin D1 expression in both bone-related and extramedullary tumors (p>0.05, Fisher's exact test).

In situ hybridization for EBER

Thirty-seven cases were available for EBER in situ hybridization study. Positivity was observed in only 1/37 (2.7%) case. In this case, the patient was a 58-year-old HIV-positive male presenting with a nasal mass. The tumor was histologically classified as intermediate grade with polymorphous feature and expressed cyclin D1 (Fig. 4).

Discussion

In the present study, the authors found that the majority of mass-forming plasma cell tumors were PCM-related. About one third of the PCM-related tumors presented with extramedullary masses. When comparing PCMs with extramedullary masses to PCMs with bone-related tumors, the authors found that both groups were not different in demographic data, HIV status, clinical presentations of PCM, extent of marrow involvement by neoplastic plasma cells and Bartl morphologic grade of the tumor cells (p>0.05). In contrast to the data reported in the literatures that extramedullary PCMs are usually found in advanced disease or relapse after treatment with immunomodulatory agents, thalidomide and/or stem cell transplant[1-3,12,13], almost half of PCMs with extramedullary involvement in the current studied population were newly diagnosed cases with low to moderate tumor burden (Durie & Salmon stage I or II). For CD56 expression, the authors found that the numbers of CD56-positive PCMs were almost half of the positive cases in previous study by Seegmiller

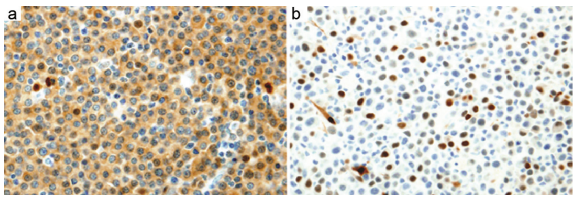

Fig. 3 Immunohistochemical staining patterns of cyclin D1 in neoplastic plasma cells. Two distinct patterns identified: (a) diffuse nuclear and cytoplasmic staining and (b) patchy nuclear staining.

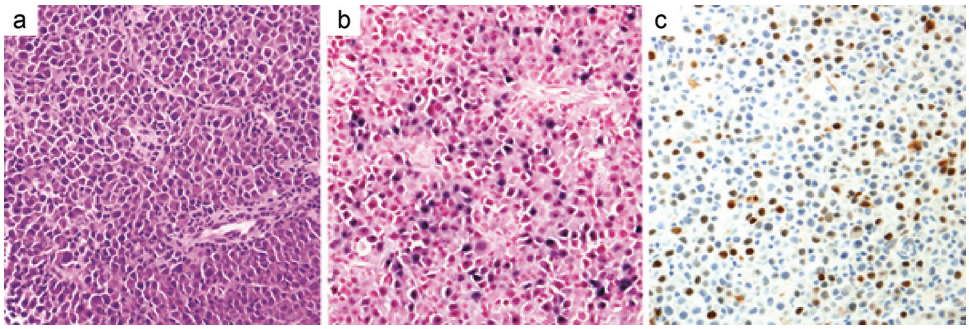

Fig. 4 Nasal extramedullary plasmacytoma with EBV association. (a) Neoplastic plasma cells showing intermediate grade morphology with polymorphous feature (H&E x400). (b) EBER in situ hybridization signals detected in the majority of neoplastic plasma cells. (c) Immunohistochemical staining for cyclin D1 showing patchy nuclear staining pattern.

et al (46.7% vs. 71%) using flow cytometry as a technique for antigen detection[4]. The authors assumed that the difference in CD56 positivity might be due to a different method of antigen detection and that flow cytometry might be superior to immunohistochemistry in detecting aberrant CD56 expression on the neoplastic plasma cells. Although Katodritou et al[13] and Cerny et al[12] reported that neoplastic plasma cells from PCM-related extramedullary masses usually displayed CD56 negativity comparing to neoplastic plasma cells from bone-related tumors, the current study failed to confirm their speculations since no association between CD56 expression in neoplastic plasma cells and tumor site was demonstrated. The data on cyclin D1 expression in neoplastic plasma cells showed that 56.7% of the PCMs were cyclin D1-positive; the percentage of cyclin D1-positive cases accorded to that reported by Lin P[14]. As reported by Kremer et al[15], the present study found no correlation between cyclin D1 expression in neoplastic plasma cells and site of mass lesion in mass-forming PCM.

OP or solitary plasmacytoma of bone is a localized bone tumor consisting of monoclonal plasma cells. Virtually, OP is identical to PCM except for evidence of bone marrow involvement at other sites and clinical features of PCM. For extramedullary plasmacytomas (EMPs), which are localized plasma cell tumors that originate outside of the bone marrow, they seem to be biologically distinct from OP and PCM[16]. In the present study, most of the OP cases complied with the epidemiological data, clinical features, and morphology previously described for the disease except for a few unusual cases that occurred in young adults and HIV-positive patients. Percentages of CD56 and cyclin D1 negativity was higher in OPs comparing to bone-related PCMs; however, the authors were not able to confirm their roles in distinguishing between the two different groups of bone-related PCNs. Of three EMPs identified in the current study, there were some interesting characteristics that have not been described in the previous studies[15,17]. These included a possible association with HIV infection and a higher percentage of cases with intermediate-grade morphology of tumor cells. Besides, the percentage of cyclin D1 positivity in EMPs in the studied population was much higher (2/3 cases; 66.67%) compared to that reported by Zuo et al[17] and Kremer et al[15]. Although EMPs seemed to show CD56 negativity and relatively high percentage of cyclin D1 positivity, the present study could not confirm the usefulness of these markers in distinguishing between EMP and extramedullary PCM.

EBV association has been reported in plasma cell tumors in both immunocompetent and immunocompromised patients[5,18-29]. In the current study, the authors identified an EBER-positive nasal EMP in a 58-year-old, HIV-infected male. The diagnosis was made based on lack of plasmablastic feature and cyclin D1 positivity in the tumor cells. To our knowledge, none of EBV-associated plasma cell tumors has been reported to express cyclin D1. This case is the first to report this phenomenon in EBV-associated plasma cell tumors. For PCM-related tumors and OPs, no EBV association was demonstrated.

In conclusion, the majority of mass-forming plasma cell tumors in Thai patients in Siriraj Hospital are PCM-related. The morphologic finding that is common to all types of plasma cell tumors is intermediate-grade morphology according to Bartl grading system. Although CD56 and cyclin D1 seem to express in PCMs more frequent than other types of plasma cell tumors, the current study cannot confirm

a value of these markers in discrimination between types of plasma cell tumors possibly due to small size of the studied population. Further study with larger recruited population is needed to clarify this subject. Identification of EBV in a case of EMP in the current study suggests that EBV association in plasma cell tumor can be encountered in Thais.

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Potential conflicts of interest

None.

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มะเร็งพลาสมาเซลล์ที่มีก้อนเป็นอาการแสดงหลัก: การศึกษาพยาธิสภาพ การแสดงออกของ CD56 และ Cyclin D1 และการตรวจพบไวรัส Epstein-Barr ในผู้ป่วยชาวไทย 39 ราย ในโรงพยาบาลศิริราช

วิริยา พิพัฒน์สกุลโรจน์, คณาพร ปราชญ์นิวัฒน์, จิตสุภา ตรีทิพย์สถิตย์

ภูมิหลัง: *มะเร็งพลาสมาเซลล์ที่มีก้อนเป็นอาการแสดงหลักพบไม่บ่อย การศึกษาก่อนหน้านี้พบว่ามะเร็งกลุ่มนี้มีความหลากหลายด้านพยาธิสภาพ การแสดงออกของ CD56 และ cyclin D1 รวมถึงความสัมพันธ์กับการตรวจพบไวรัส Epstein-Barr โดยลักษณะที่พบเหล่านี้อาจมีบทบาทในการช่วยวินิจฉัยชนิดของมะเร็งพลาสมาเซลล์ ปัจจุบันยังไม่มีข้อมูลดังที่กล่าวมาข้างต้นในผู้ป่วยชาวไทย*

วัตถุประสงค์: *เพื่อศึกษาพยาธิสภาพ การแสดงออกของ CD56 และ Cyclin D1 และการตรวจพบไวรัส Epstein-Barr ในมะเร็งพลาสมาเซลล์ที่มีก้อนเป็นอาการแสดงหลัก*

วัสดุและวิธีการ: *ชิ้นเนื้อจากมะเร็งพลาสมาเซลล์ที่มีก้อนเป็นอาการแสดงหลัก 39 ราย ที่ได้รับการวินิจฉัยในช่วงปี พ.ศ. 2549-2553 ในโรงพยาบาลศิริราช และมีเนื้อเพียงพอสำหรับการศึกษาด้วยเทคนิค tissue microarray ถูกนำมาทบทวนลักษณะทางจุลพยาธิวิทยาและแบ่งชนิดตามระบบ Bartl หลังจากนั้นจึงสร้าง tissue microarray จากชิ้นเนื้อ และนำไปศึกษาการแสดงออกของ CD56 และ cyclin D1 และตรวจหาไวรัส Epstein-Barr ด้วยเทคนิคอิมมูโนฮิสโตเคมี และ in situ hybridization ตามลำดับ*

ผลการศึกษา: *ชิ้นเนื้อมะเร็งพลาสมาเซลล์ที่มีก้อนเป็นอาการแสดงหลัก 39 ราย เป็นมะเร็งพลาสมาเซลล์ชนิดมัยอีโลม่า 31 ราย ชนิดพลาสมาซัยโตม่าที่เกิดในกระดูก 5 ราย และชนิดพลาสมาซัยโตม่าที่เกิดนอกไขกระดูก 3 ราย การศึกษานี้พบว่าเซลล์มะเร็งที่มีลักษณะ intermediate grade พบบ่อยที่สุดในมะเร็งพลาสมาเซลล์ทุกชนิด แม้ว่ามะเร็งพลาสมาเซลล์ชนิดมัยอีโลม่าจะมีการแสดงออกของ CD56 และ cyclin D1 มากกว่าชนิดอื่น แต่ความแตกต่างในการแสดงออกดังกล่าวไม่มีนัยสำคัญทางสถิติ ($p>0.05$) ในการตรวจหาไวรัส Epstein-Barr พบไวรัสดังกล่าวในมะเร็งพลาสมาเซลล์ชนิดพลาสมาซัยโตม่าที่เกิดนอกไขกระดูก 1 ราย*

สรุป: *ในผู้ป่วยชาวไทย 39 ราย ของโรงพยาบาลศิริราช พบว่ามะเร็งพลาสมาเซลล์ที่มีก้อนเป็นอาการแสดงหลักส่วนใหญ่เป็นชนิดมัยอีโลม่า เซลล์มะเร็งส่วนใหญ่มีลักษณะที่จัดอยู่ในกลุ่ม intermediate grade ตามระบบ Bartl เนื่องจากประชากรในการศึกษาครั้งนี้มีจำนวนน้อยจึงไม่สามารถสรุปบทบาทของ CD56 และ cyclin D1 ในการช่วยวินิจฉัยชนิดของมะเร็งพลาสมาเซลล์ได้ การตรวจพบไวรัส Epstein-Barr ในมะเร็งพลาสมาเซลล์ชนิดพลาสมาซัยโตม่าที่เกิดนอกไขกระดูกในการศึกษานี้อาจบ่งถึงโอกาสในการพบไวรัส Epstein-Barr ในมะเร็งพลาสมาเซลล์ในผู้ป่วยชาวไทย*