

Original Article

MYD88 L265P mutation status in small B-cell lymphoma with plasmacytic differentiation and extensive amyloid depositionSanya Sukpanichnant¹, Monthatip Pinijvechagam² and Naravat Pongvarin³¹Department of Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University; ²Division of Hematology, Department of Medicine, Police General Hospital, Bangkok; ³Department of Clinical Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University**Abstract:**

Background: MYD88 L265P mutation has been used to distinguish lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia (LPL/WM) from marginal zone lymphoma (MZL) with plasmacytic differentiation (PCD). This determination is helpful when clinical findings cannot separate out these 2 entities. But the prevalence of MYD88 L265P mutation and its association with small B-cell lymphoma with PCD (SBCL-PCD) and extensive amyloid deposition, a rare condition, is not known. **Materials and Methods:** Retrospective study of SBCL-PCD and extensive amyloid deposition was subject to detection for MYD88 L265P mutation. **Results:** Total of 10 cases (5 each with systemic or localized disease) were included in the study. Only one case with systemic disease had MYD88 L265P mutation. **Conclusion:** Most cases of SBCL-PCD and extensive amyloid deposition do not show MYD88 L265P mutation, suggestive of MZL with PCD over LPL/WM.

Keywords : ● MYD88 L265P mutation ● Waldenstrom macroglobulinemia ● Small B-cell lymphoma
● Plasmacytic differentiation ● Amyloid

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นิพนธ์ต้นฉบับ

สถานภาพการกลายพันธุ์ *MYD88* L265P ในมะเร็งต่อมน้ำเหลืองชนิดบีเซลล์ขนาดเล็กที่มีการเปลี่ยนสภาพเป็นเซลล์พลาสมา ร่วมกับการพอกของแอมิลอยด์จำนวนมาก

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บทคัดย่อ

ความเป็นมา การกลายพันธุ์ *MYD88* L265P ได้นำมาใช้แยกมะเร็งต่อมน้ำเหลืองชนิดลิมโฟพลาสมาซิติค/วอลเดนสตรอม มาโครโกลบูลินนีเมีย (แอลพีแอล/ดับเบิลยูเอ็ม) จากมะเร็งต่อมน้ำเหลืองชนิดมาร์จินัลโซน (เอ็มแซดแอล) ที่มีการเปลี่ยนสภาพเป็นเซลล์พลาสมา (พีซีดี) การตรวจหาการกลายพันธุ์นี้มีประโยชน์เมื่อสิ่งตรวจพบทางคลินิกไม่สามารถแยกทั้งสองโรคนี้ออกจากกันได้ แต่ความชุกของการกลายพันธุ์ *MYD88* L265P และความเกี่ยวข้องกับมะเร็งต่อมน้ำเหลืองชนิดบีเซลล์ขนาดเล็กที่มีการเปลี่ยนสภาพเป็นเซลล์พลาสมา ร่วมกับการพอกของแอมิลอยด์จำนวนมาก (เอลบีซีแอล-พีซีดี) ซึ่งพบได้น้อย ยังไม่ทราบกัน **วิธีการ** การศึกษาย้อนหลังในเอลบีซีแอล-พีซีดีเพื่อตรวจพบการกลายพันธุ์ *MYD88* L265P **ผลการศึกษา** มีทั้งหมด 10 รายที่นำมาศึกษา ตรวจพบการกลายพันธุ์ *MYD88* L265P เพียงรายเดียวที่มีโรคทั่วร่างกาย **สรุป** เอลบีซีแอล-พีซีดีส่วนใหญ่ไม่พบการกลายพันธุ์ *MYD88* L265P ซึ่งแนะนำว่าจะเป็นเอ็มแซดแอลที่มีพีซีดี มากกว่าแอลพีแอล/ดับเบิลยูเอ็ม

คำสำคัญ : ● การกลายพันธุ์ *MYD88* L265P ● วอลเดนสตรอม มาโครโกลบูลินนีเมีย ● มะเร็งต่อมน้ำเหลืองชนิดบีเซลล์ขนาดเล็ก ● การเปลี่ยนสภาพเป็นเซลล์พลาสมา ● แอมิลอยด์

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต. 2563;30:369-78.

Introduction

According to Amyloid Nomenclature 2018,¹ amyloid is defined histologically as extracellular deposits of protein fibrils showing green-yellow (apple green) birefringence under polarizing microscopy after Congo red staining. At present, there are 36 human amyloid proteins, two of which — amyloid light chain (AL) and amyloid heavy chain (AH) — can be associated with localized or systemic disease. AL is the most common type of immunoglobulin-associated amyloidosis, also known as AL amyloidosis. When amyloid deposit is localized leading to the formation of a tumor-like lesion, the term “amyloidoma” may be used. In clinical practice, after amyloid deposit is verified in tissue biopsy, physicians should separate AL amyloidosis from other types — for example serum amyloid A (AA amyloidosis).² Immunoglobulin light chain amyloidosis or AL amyloidosis requires laboratory investigation to demonstrate clonal plasma cells in marrow or in tissue that may turn out to be plasma cell myeloma or small B-cell lymphoid neoplasm with plasmacytic differentiation.³

Amyloidosis is associated with plasma cell myeloma in approximately 10-15% of cases,⁴ however, it is a rare condition in B-cell lymphoma and its clinical features and disease progression have still not been well characterized. Moreover, it has been reported in some small case series,⁵⁻⁷ particularly in lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia (LPL/WM),⁸⁻¹¹ chronic lymphocytic lymphoma/small lymphocytic lymphoma (CLL/SLL),^{12,13} and marginal zone lymphoma (MZL).¹⁴⁻¹⁷

Small B-cell lymphoma with plasmacytic differentiation (SBCL-PCD) is still a challenge to diagnose because it encompasses various subtypes that share morphologic and immunophenotypic similarities, especially LPL/WM and MZL. Recently, a recurrent mutation was noted in the myeloid differentiation primary response 88 gene (*MYD88* L265P), an adaptor protein in nuclear factor kappa B (NF- κ B) and mitogen activated protein kinase (MAPK) signaling pathway, which play a role in cell proliferation and survival, immune regulation and

also tumor genesis. *MYD88* L265P mutation is found in approximately 90-100% of LPL/WM and it seems to be a promising way to distinguish LPL/WM from other SBCL-PCD. Since the *MYD88* L265P mutation is absent in plasma cell myeloma (PCM), follicular lymphoma (FL) and mantle cell lymphoma (MCL), it can be found in 54% of IgM monoclonal gammopathy of undetermined significance (MGUS), 4-5% of splenic marginal zone lymphoma (SMZL), 7-9% of extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma), 6.7% of ocular adnexal extranodal marginal zone lymphoma and 2.9-4% of CLL/SLL.¹⁸⁻²⁵ Recently, Chakraborty et al. reported 10 out of 14 cases of IgM amyloidosis with *MYD88* L265P mutation in which four cases had prior diagnosis of WM while nine out of 10 had clonal B lymphocytes in bone marrow which indicated association of *MYD88* L265P mutation with lymphoproliferative disorder.²⁶

After excluding CLL/SLL, FL and MCL, a number of SBCL-PCD and amyloid deposition did not have a definite diagnosis for the subtype. In this study, we tried to identify the prevalence of *MYD88* L265P mutation and its association in SBCL-PCD and extensive amyloid deposition.

Materials and Methods

This study was conducted after a certificate of approval (Si545/2018) was issued by the Institutional Review Board at the Faculty of Medicine Siriraj Hospital, Mahidol University for research project no. 531/2561(EC2) using information in clinical records and repository samples, including slides and tissue blocks. Clinical information, including the results of serum immunoglobulin and serum free light chain studies, was reviewed from the patients' clinical records.

Subject selection and study design

Retrospectively, 15 cases diagnosed with SBCL-PCD and extensive amyloid deposition were identified from the HCLAB computer database system at the Department of Pathology, Faculty of Medicine Siriraj Hospital, Mahidol

University from January 2006 to December 2018. Histology and immunohistochemistry (IHC) of the included cases were reviewed by two hematopathologists (SS & MP) and additional IHC was checked in each case to make the diagnosis as per WHO classification of tumors of haematopoietic and lymphoid tissues, revised 4th edition, 2017.¹⁸ The IHC study panel included available commercial antibodies against CD3, CD5, CD10, CD20, CD23, CD38, CD138, Cyclin D1, MUM-1, Bcl2, Bcl6, kappa, lambda, IgG, IgA and IgM to classify the subtype of lymphoma. Cases with definite immunophenotype of CLL/SLL, MCL, FL, PCM or MGUS were excluded. Amyloidosis was defined by a positive Congo red stain and the presence of apple green birefringence under polarized light microscope.

DNA extraction

The formalin-fixed paraffin-embedded tissue was cut into eight 10 µm thick and deparaffinized sections using xylene and 100% ethanol. The DNA extraction was performed using the QIAamp® DNA FFPE Tissue kit (Qaigen group, Germany) according to the manufacturer's protocol. The DNA concentrations were tested using the ThermoScientific Nano drop 2000 spectrophotometer.

The MYD88 L265P mutation detection

Tests to detect the presence of the MYD88 L265P mutation were performed using the qBiomarker Somatic Mutation PCR assay (Qaigen, Germany) with wild-type sample (tonsil with reactive lymphoid hyperplasia) and a positive sample (a known case of LPL, kindly provided by the molecular genetic laboratory at Department of Pathology, Faculty of Medicine Ramathibodi Hospital, Mahidol University) as control subjects. Meanwhile, a PCR reaction was performed using QIAGEN Roter-Gene Q cyclers for 40 cycles with every step followed strictly as defined in the protocol instructions.

Results

Demographic data

A total of 15 cases with diagnosis of SBCL-PCD and extensive amyloid deposition were identified from a

computer database system, however, only 10 cases were included in the study after five were excluded due to no available paraffin embedded tissue (3 cases), change of the diagnosis to plasma cell myeloma (1 case) and lack of apple green birefringence under polarized light (1 case). Histologic evaluation revealed sparse small lymphoid cells and lymphoplasmacytoid cells within extensive amyloid deposition in all cases proven to have light chain-restricted B-cells with CD20+, CD3-, CD5-, CD10-, CD23-, cyclin D1- immunophenotype and a low proliferation index by Ki-67. (Figures 1 & 2)

The patients' characteristics were listed in Table 1. Females accounted for 60% of patients with a median age of 55 at diagnosis. Lymph node was the most common site of involvement, followed by skin. The IHC study also demonstrated that 50% of cases had kappa light chain restriction. Only 4 cases demonstrated immunoglobulin heavy chain by IHC (2 cases with IgM and 2 cases with IgG).

Five cases (no. 1 to 5) had systemic disease but 2 of them (no. 3 & 4) were investigated further for serum protein electrophoresis (SPEP) and serum free light chain (SFLC). Yet, only 1 case (no. 4) demonstrated lambda light chain disease, however, no serum M-protein was detected. The other 5 cases (no. 6 to 10) had localized disease; 4 of them (no. 6 to 9) were investigated for SPEP that were negative for serum M-protein and SFLC showed polyclonal pattern. A bone marrow study was obtained in 6 cases (3 systemic and 3 localized cases); only 1 systemic case (no. 1) was positive while the others were negative for lymphoma involvement.

MYD88 L265P mutation status

Testing for the MYD88 L2656P mutation could be performed in 9 cases. One sample had to be excluded due to a small biopsy and poor quality of the extracted DNA (no. 7). Allele specific PCR for MYD88 L265P mutation was performed in these 9 cases with wild type and positive control for comparison. Only 1 case (no. 2) showed a positive result at 35 cycles (Figure 3). Case no. 2 had systemic disease with IgM/kappa by IHC

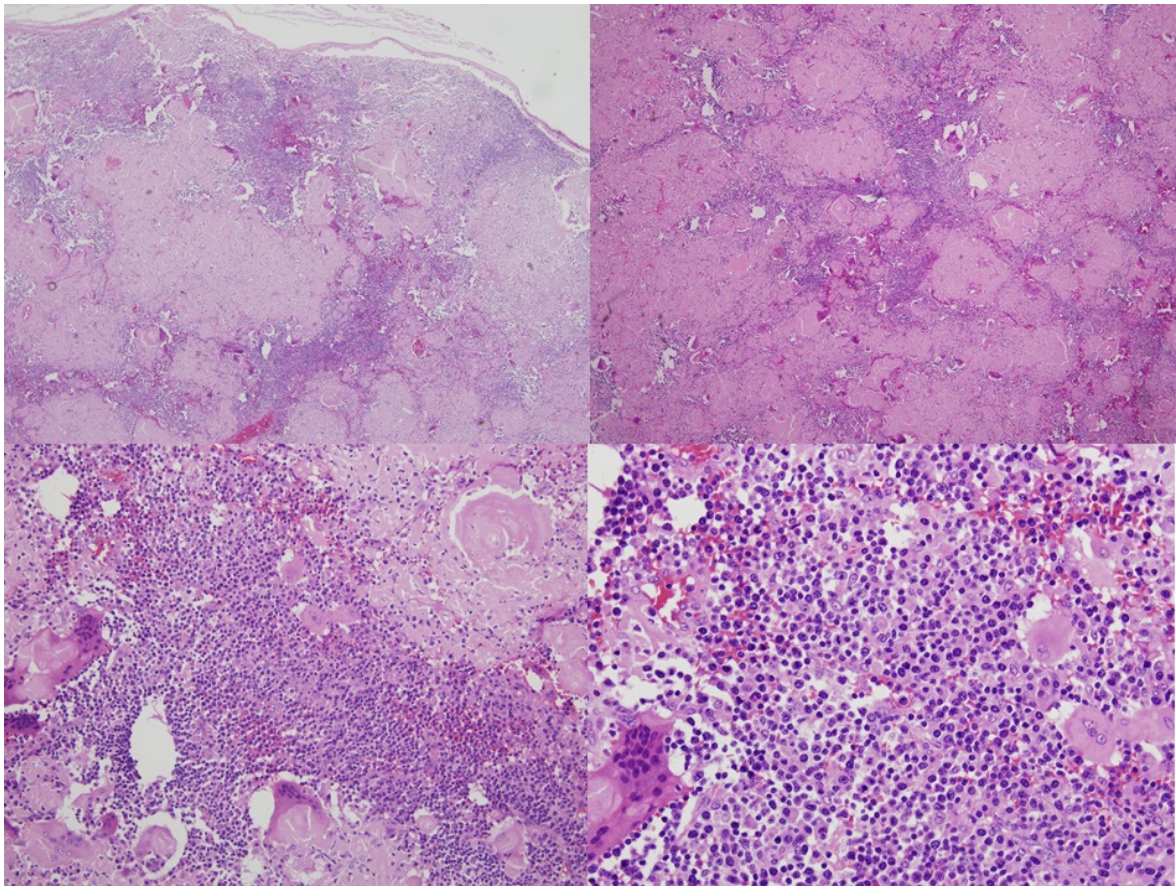


Figure 1 Lymph node of the patient demonstrates infiltration by small lymphoid cells and lymphoplasmacytoid cells with extensive amyloid deposition (pink amorphous materials) and scattered foreign body-typed multinucleated giant cells.

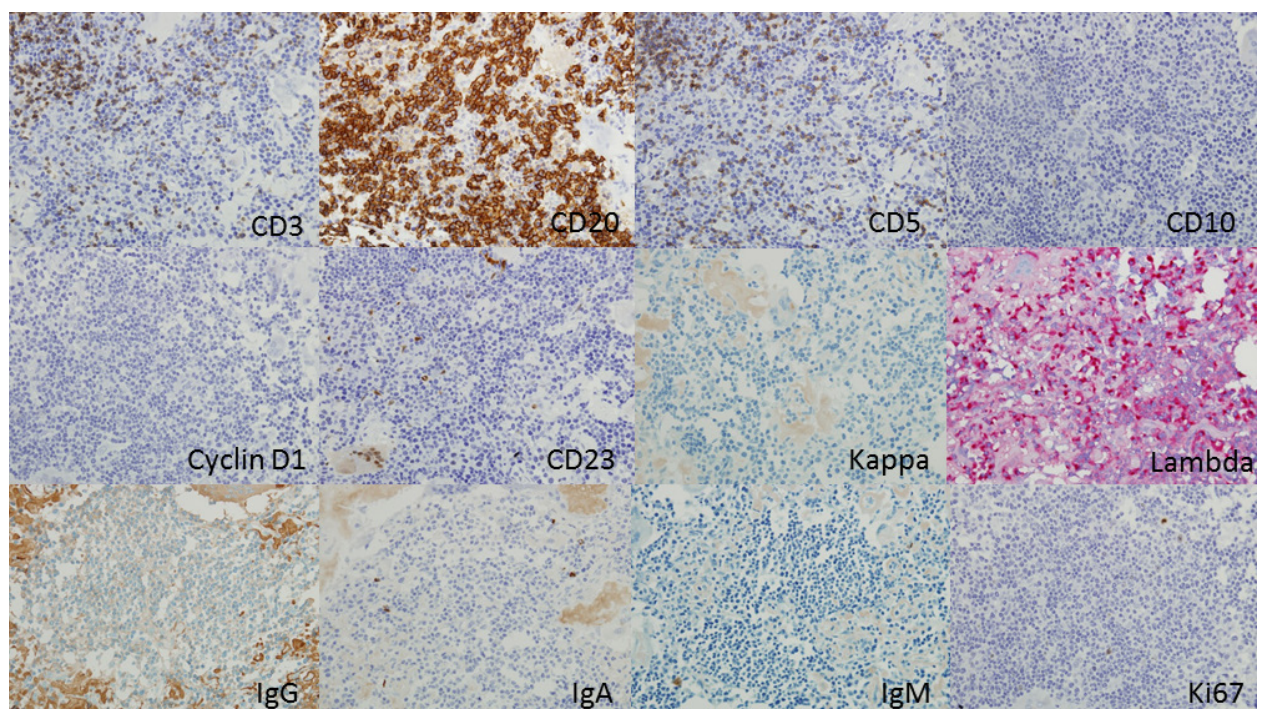


Figure 2 Immunohistochemistry shows lambda light chain (red-colored cytoplasmic positivity) restricted CD20+ (brown-colored membrane positivity) small neoplastic B-cells.

Table 1 Characters of the 10 patients with small B-cell lymphoma with plasmacytic differentiation and extensive amyloid deposition

Case No.	Gender	Age	Organ	IHC heavy chain	IHC light chain	Congo red	SPEP	SFLC	Bone marrow staging	Systemic/ localized disease
1	female	51	Marrow	-	Lambda	+	N/A	N/A	+	S
2	male	73	LN	IgM	Kappa	+	N/A	N/A	N/A	S
3	female	41	LN	IgM	Kappa	+	-	PC	-	S
4	male	56	spleen	-	Lambda	+	-	Lambda	-	S
5	female	47	trachea	N/A	Kappa	+	N/A	N/A	N/A	S
6	female	58	skin	IgG	Kappa	+	-	PC	-	L
7	male	25	skin	-	Kappa	+	-	PC	N/A	L
8	female	66	skin	IgG	Lambda	+	-	PC	-	L
9	male	61	LN	-	Lambda	+	-	PC	-	L
10	female	70	LN	-	Lambda	+	N/A	N/A	N/A	L

IHC: immunohistochemical study; L: localized disease; N/A: not available; PC: polyclonal; S: systemic disease;

SFLC: serum free light chain; SPEP: serum protein electrophoresis

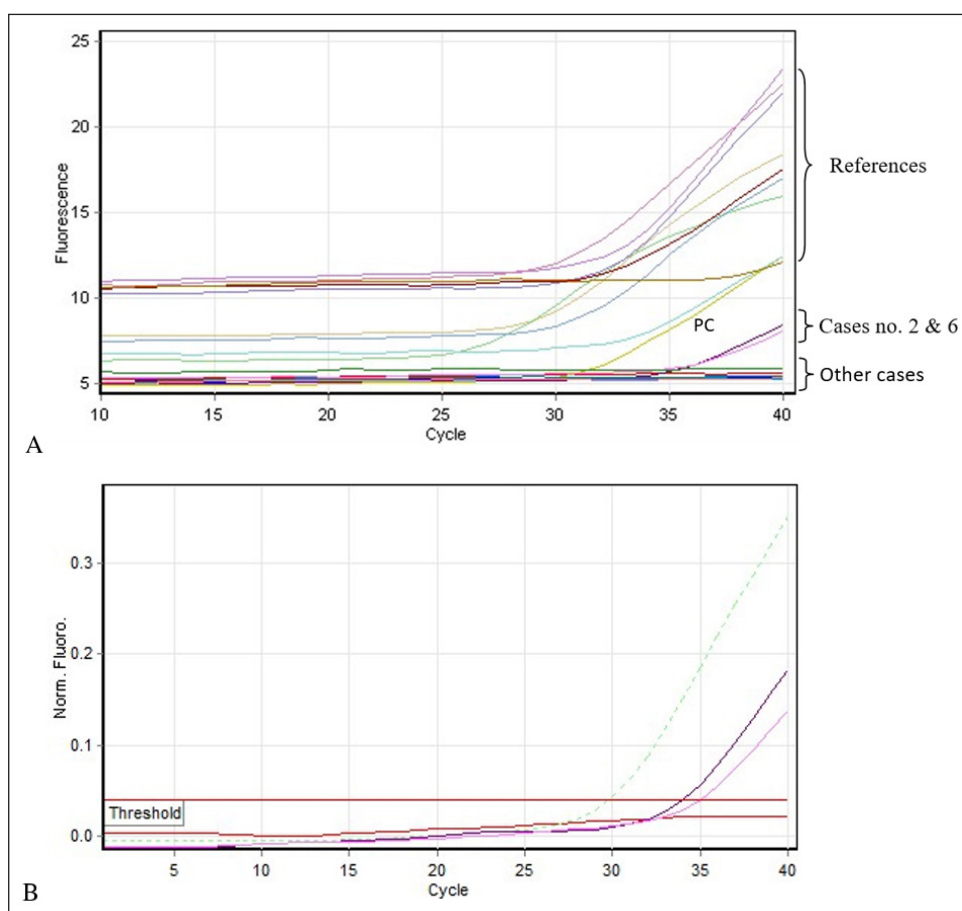


Figure 3 **A)** Allele specific PCR for *MYD88* L265P mutation performed in 9 cases with positive and wild type control for comparison. Note *MYD88* L265P mutation in case no. 2 (deep purple) and suspected one in case no. 6 (pink) after 35 cycles. **B)** Rerun of samples from case no. 2 and 6 with control (green dots) shows that only case no. 2 is acceptable for *MYD88* L265P mutation.

study of the lymph node but unfortunately, no SPEP, SFLC, or marrow staging was performed because the patient was referred back to a provincial hospital after the pathologic diagnosis was given. Case no. 6 was interpreted as negative after a rerun of the test. This particular case had localized disease with IgG/kappa by IHC study of the skin tumor mass (6x5 cm. at lower extremity). No serum M-protein was detected by SPEP. Polyclonal pattern was noted in SFLC and marrow staging was negative for lymphoma involvement.

Discussion

Amyloidosis associated with B-cell non-Hodgkin lymphomas (NHLs) is a rare complication and it has been described in only 2-4% of all cases. A clear picture of this association has not yet been established in terms of clinical features, treatment strategy, or clinical outcome due to the rare occurrence of the association. Upon review of literature and case reports, LPL/WM and MALT lymphoma — in addition to plasma cell myeloma — has been reported to be frequently associated with amyloidosis when compared to other types of lymphoproliferative disorders.^{5-11,14-17,27-31} In 1993, Gertz et al. reported 50 cases of IgM monoclonal gammopathy with primary systemic amyloidosis. In this series, 10 cases had a diagnosis of WM while 11 cases had lymphoma or lymphoproliferative disorder.⁸ Meanwhile, Telio et al. reported that 10 patients could be divided into two distinct syndromes of lymphoma-associated amyloidosis. One syndrome was lymphoma with peritumoral amyloidosis which lacked or had low serum M-protein detection with localized organ involvement, eventually leading to diagnosis of MALT lymphoma. The other syndrome was systemic amyloidosis with high level of M-protein and multi-organ involvement that eventually led to diagnosis of LPL/WM with an inferior outcome.⁵ Last but not least, Ryan et al. described 20 cases of MALT lymphoma with amyloid deposition and referred to cases with predominant amyloid as “amyloidoma-like lymphoma” (amyloid deposits > 50% of tumor). The

masses were often bulky and occurred in soft tissue, skin, lung, head and the neck region. The majority of cases had an indolent clinical course and amyloidosis did not seem to be associated with poor prognosis.¹⁵

In our study, all 10 patients had histologic features of peritumoral extensive amyloidosis with sparse B-cell lymphoplasmacytic infiltration or amyloidoma-like lymphoma according to study by Ryan et al.¹⁵ No predilection of light chain restriction was noted among the 10 cases (kappa 5 cases and lambda 5 cases). SPEP was performed in six cases but none had the serum M-protein. Four of the patients repeated the study with serum immunofixation and the results remained negative.

While 5 cases displayed systemic symptoms, only 2 cases had serum M-protein build-up with the other 3 cases referred back to the provincial hospital. Only 1 case (no. 4) had lambda light chain disease with severe symptoms of systemic amyloidosis leading to a splenectomy being performed. However, MYD88 L265P mutation in this particular case was not detected.

In our study, 9 of the 10 cases were tested for the presence of the MYD88 L265P mutation. Only 1 case (no. 2) had the MYD88 L265P mutation. Case no. 2 seemed to be LPL/WM due to the presence of the MYD88 L265P mutation. Meanwhile, case no. 6 was interpreted as negative for MYD88 L265P mutation as it was quite similar to primary cutaneous MZL with massive amyloid deposition in the tumor mass as described in literature.^{28,29} Stuhlmann-Laeisz et al. tested a large cohort of 29 cases with the purpose of finding a distinct entity of AL amyloidosis with localized B-cell neoplasm of undetermined significance. Histologic findings in the study revealed sparse clonal plasma cells and B-cell with marginal zone phenotype together with amyloidosis. Among 18 of the 29 patients for whom there was clinical data, 5 cases had systemic disease. The MYD88 L265P mutation was tested in all cases and only 1 case showed a positive result (but no available information to decide about localized or systemic disease) so the authors suggested the differential diagnosis of

secondary infiltration of the lymph node by LPL/WM or IgM-MGUS.³² Similarly, our study showed *MYD88* L265P mutation in only one of the 9 cases tested. Thus, based on these 2 studies, most cases of SBCL-PCD and extensive amyloid deposition do not show *MYD88* L265P mutation, suggestive of MZL with PCD over LPL/WM.

The last issue to address about our study is the rarity of SBCL-PCD and extensive amyloid deposition when compared to the frequency of MALT lymphoma reported from the previous studies. The first study from our institution in 2004 according to the WHO classification 2001, 76 cases of MALT lymphoma were reported among 1,983 cases of malignant lymphoma or 1,826 cases of NHLs (3.8% of all malignant lymphoma and 4.2% of NHLs, respectively) during the 9-year period from August 1, 1993 to July 31, 2002 and it was ranked no. 4 among the most common types of lymphoma at that time.³³ The second study from the nationwide Thai Lymphoma Study Group according to the WHO classification 2008, extranodal MALT lymphoma constituted 5.2% of all 4,056 NHLs during the 8-year period from January 2007 to December 2014 and it was ranked no. 3 among the most common types of NHLs at that time.³⁴ Thus, the expected total cases of MALT lymphoma during the period of study varied from 111 to 343 cases so that the 10 cases of SBCL-PCD and extensive amyloid deposition in our study constituted only 3 to 9% of all MALT lymphoma.

Conclusion

Careful evaluation is needed in order to make diagnosis of SBCL-PCD and extensive amyloid deposition. Clinical information including laboratory findings, especially serum immunoglobulin, histology, IHC study and molecular analysis should be gathered to make a diagnosis. Any case presenting systemic disease and paraproteinemia should be aware of LPL/WM and test for *MYD88* L265P mutation if possible. Then, diagnosis of LPL/WM can be established with the support of *MYD88* L265P mutation.

Based on the study by Stuhlmann-Laeisz et al.³² and our study, however, *MYD88* L265P mutation is uncommon in SBCL-PCD and extensive amyloid deposition. So, when *MYD88* L265P mutation cannot be evaluated, the diagnosis should rely on clinical information and LPL/WM can be diagnosed only in case with typical findings of WM while the others should be treated as MZL with PCD.

Conflict of interest statement

All authors declare that they have no conflict of interest.

Acknowledgments

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Contributions

SS contributed to the study conception and design, data analysis, writing the manuscript, manuscript approval (45%)

MP contributed to the study conception and design, material preparation, data collection, data analysis, drafting the manuscript, and manuscript approval (40%)

NP contributed to the study conception and design, confirming the genetic result interpretation, data analysis, and manuscript approval (15%)

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