Original Article

Bone Marrow Involvement in Lymphoma: Study from Northern Thailand

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Background: Lymphomas have a pattern preference in bone marrow involvement (BMI) that helps in diagnosis, however, studies on the pattern of BMI show different results across the regions.

Objective: To determine the prevalence of lymphomas with and without BMI, and evaluate the percentage, the patterns, and the discordance in cases with marrow involvement.

Materials and Methods: Data from 1,083 newly diagnosed lymphoma patients in Maharaj Nakorn Chiang Mai Hospital between January 2013 and December 2020 were evaluated for BMI. The 267 patients with BMI were analyzed for prevalence. The available slides from 260 patients were assessed for percentage, patterns, and discordance.

Results: The prevalence of BMI in non-Hodgkin lymphoma (NHL) was 255/1,014 (25.1%), with B-cell NHL it was 239/902 (26.5%), and T-cell NHL was 16/112 (14.3%), while the prevalence of BMI in Hodgkin lymphoma (HL) was 12/69 (17.4%). The prevalence of BMI was highest in patients with lymphoplasmacytic lymphoma (LPL) at 92.3%, followed by Burkitt lymphoma (BL) at 75.0%, and mantle cell lymphoma at 73.3%. The most common pattern was interstitial. A diffuse pattern was most common in BL and diffuse large B-cell lymphoma (DLBCL). A mixed pattern was most common in LPL. A paratrabecular pattern was most common in follicular lymphoma. HL usually had a pattern of Reed-Sternberg cells with a characteristic background. The discordant DLBCL was 12.4% (15/121) cases and patients with discordant DLBCL tended to have a superior overall survival.

Conclusion: Each subtype of lymphoma has a different tendency to involve bone marrow and have a preference in patterns of involvement. These can provide a differential diagnosis of the subtypes of lymphoma. The discordant lymphoma is likely to have a better prognosis than the concordant one. This might affect the future treatment.

Keywords: Bone marrow; Lymphoma; Pattern; Bone marrow involvement; Discordance

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Bone marrow biopsy, a procedure to collect and examine bone marrow, is important for evaluating patients with non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL). The percentage of bone marrow involvement (BMI) in NHL and HL has been reported in 8% to 100%[1,2], and 3% to 15%[3], respectively. Nowadays, many institutes have implemented fluorodeoxyglucose positron emission tomography (PET) to evaluate BMI as a non-invasive procedure[2]. In Thailand, a PET scan is not widely available in most hospitals, so bone marrow examination is still the essential procedure for staging[3,4].

Patients with marrow involvement in lymphoma are indicated as stage IV and have more adverse outcomes[5,6]. The morphology, architectural pattern, and immunohistochemistry help identify the lesions in the bone marrow. In addition, they can provide a differential diagnosis because subtypes of lymphomas have a preference in the pattern of involvement[7,8]. For example, the paratrabecular pattern and the intrasinusoidal pattern of BMI have been reported to be associated with follicular lymphoma (FL) and splenic marginal zone lymphoma[8], respectively. In some studies, patients with diffuse large B-cell lymphoma (DLBCL) and concordant BMI had inferior overall survival compared to those with discordant BMI[2].

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Table 1. Summary of previous studies

Country	Highest number of cases with BMI	Most common pattern of BMI	Brief results	Reference
United States of America	FL	Mixed	- Paratrabecular pattern was associated with FL. - Diffuse pattern was most common in DLBCL and BL. - Interstitial pattern was most associated with LPL.	7
England	FL	Paratrabecular	- Paratrabecular pattern was associated with FL. - Diffuse pattern was most common in DLBCL and BL. - MZL and LPL showed even distribution of each pattern. - Most MCL showed diffuse or nodular patterns. - HL mostly showed a diffuse pattern.	8
China	MCL	Mixed	- MCL, T-LBL, and SLL most likely involved marrow in a diffuse pattern. - Focal pattern (clusters of irregularly outlined tumor cells) was often seen in DLBCL. - Paratrabecular pattern was associated with FL. - HL was always accompanied by a characteristic background.	12

BMI=bone marrow involvement; BL=Burkitt lymphoma; DLBCL=diffuse large B-cell lymphoma; FL=follicular lymphoma; HL=Hodgkin lymphoma; LPL=lymphoplasmacytic lymphoma; MCL=mantle cell lymphoma; SLL=small lymphocytic lymphoma; T-LBL=T-cell lymphoblastic lymphoma

Studies on the pattern of BMI in patients with lymphoma show different results across the regions as shown in Table 1. It is due to multifactorial causes including prevalence, race, and nature of the diseases. In the present study, most of the patients were from Northern Thailand. It was reported that DLBCL outnumbered other subtypes of lymphoma in the present study region[9]. Therefore, the authors expected this might affect the results about DLBCL in some aspects. The authors calculated the prevalence of BMI in lymphomas and assessed for the percentage, the patterns of involvement, and the discordance. Particularly, patients with discordant lymphoma were analyzed for progression-free survival and overall survival.

Materials and methods

Study population

One thousand eighty-three newly diagnosed patients with lymphoma having BMI in Maharaj Nakorn Chiang Mai Hospital between January 2013 and December 2020 were recruited. The present study (study code: PAT-2563-07136 / Research ID: PAT-2563-07136) was approved by the Institutional Review Board of Chiang Mai University and conducted following the Declaration of Helsinki.

Inclusion and exclusion criteria

One thousand eighty-three patients with newly diagnosed lymphoma who had a bone marrow test were included in this study. Cases presenting with leukemia symptoms, such as chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia, and hairy cell leukemia were excluded. According to the 2017, World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues, cases with features of small lymphocytic leukemia (SLL) with a lymphocytosis of less than 5,000/μL were included in the present study. Two hundred sixty-seven patients with marrow involvement by lymphoma were included. In addition, seven cases with unavailable glass slides and paraffin blocks were excluded, because patients were referred to the other hospitals. Therefore, 260 cases were reviewed to confirm the diagnosis, percentage of total cellularity involved by lymphoma, patterns of involvement, and discordance by the two hematopathologists. The authors approached every case with morphology (H&E stain) in conjunction with immunohistochemistry. Immunostaining on paraffin sections for B and T-cells NHL included CD20 (monoclonal L26; DAKO, dilution 1:1,000), CD3 (polyclonal; DAKO, dilution 1:500), CD5 (monoclonal 4C7; Novo, dilution 1:100), CD10 (monoclonal 56C6; Novo, dilution 1:100), CD23 (monoclonal DAK-CD23; DAKO RTU), CyclinD1 (monoclonal EP12; DAKO RTU), BCL2 (monoclonal 124; DAKO RTU), BCL6 (monoclonal LN22; Novo, dilution 1:100), CD138 (monoclonal MI15; DAKO, dilution 1:100), Kappa (polyclonal; DAKO, dilution 1:5,000), Lambda (polyclonal; DAKO, dilution 1:5,000), CD4 (monoclonal SP35; Roche), CD8 (monoclonal CD8/144B; DAKO, dilution 1:100), CD30 (monoclonal Ber-H2; DAKO RTU), PD-1 (monoclonal NAT105; Roche), CXCL13 (monoclonal 53,610; Biotech, dilution 1:100), and CD56 (monoclonal CD564; Novo, dilution 1:100). In cases with NK/T-cell lymphoma, in situ hybridization

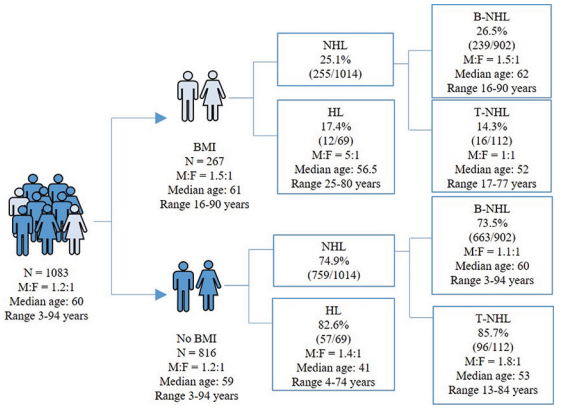

Figure 1. Overall characteristics.

BMI=bone marrow involvement; B-NHL=B-cell non-Hodgkin lymphoma; HL=Hodgkin lymphoma; NHL=non-Hodgkin lymphoma; T-NHL=T-cell non-Hodgkin lymphoma

for EBV-encoded RNA (EBER) was performed. Immunostaining on paraffin sections for Hodgkin lymphoma included CD15 (monoclonal MMA, Roche), CD30 (monoclonal Ber-H2, DAKO RTU), and PAX5 (monoclonal SP34, Roche).

Patterns of involvement

In the present study, the authors classified the patterns of involvement in NHL as diffuse, interstitial, intrasinusoidal, nodular, paratrabecular, and mixed[7,8]. The diffuse pattern was defined as areas of effacement by a dense infiltrate of lymphocytes without forming nodules. The interstitial pattern was referred to lymphoid cells infiltrating between fat cells without distorting the normal low-power architecture. The intrasinusoidal pattern, similar to the interstitial pattern, was regarded as a sharp linear infiltration highlighted by immunohistochemistry. The nodular pattern was described as circumscribed aggregates of lymphoid cells with a round to oval shape. The paratrabecular pattern was defined as lymphoid aggregation aligned alongside bony trabecula, and the mixed pattern was referred to the coexistence of two or more patterns described earlier.

For HL, the authors classified the patterns of involvement as the presence of Reed-Sternberg (RS) cells with cellular environment characteristic of HL as mixed inflammatory cells, granuloma, or fibrosis, and presence of only cellular environment characteristic of HL without definite RS cells[3].

Discordance

The discordant lymphoma was referred to two or more distinct histologic subtypes occurring in different anatomical sites, for example, nodal DLBCL had BMI with low-grade NHL. It was only possible to evaluate 248 cases with BMI excluding cases diagnosed with B-cell NHL. All statistical analyzes were performed using Stata Statistical Software, version 16.1 (StataCorp LLC, College Station, TX, USA). The endpoint of the present study was progression-free survival defined as the length of time from the date of diagnosis to the date of first documented disease progression, and overall survival defined as the length of time from the date of diagnosis to the date of documented death. The Kaplan-Meier analysis was used to estimate the probability and duration of progression-free survival and overall survival.

Results

Characteristics

Among the 1,083 patients, there were 598 males and 485 females (1.2:1 M:F ratio) with the mean age of 57.1±16.5 years, median age of 60 years, and range from 3 to 94 years.

For males, the specimens represented the patients with the mean age of 57.8±16.6 years, the median age of 60 years, and range from 6 to 92 years. For females, the specimens represented the patients with the mean age of 56.3±16.3 years, the median age of 59 years, and range from 3 to 94 years.

The overall characteristics of the present study are summarized in Figure 1.

For NHL, the most common type was DLBCL at 57.3%, followed by marginal zone lymphoma at 14.6%, and peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS) at 3.8%. The prevalence of nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) and classical HL were 0.4% and 6.0%, respectively. The results are summarized in Table 2.

The prevalence of BMI in NHL was 255/1,014 (25.1%), with B-cell NHL as 239/902 (26.5%), and T-cell NHL as 16/112 (14.3%). The prevalence of BMI in Hodgkin lymphoma was 12/69 (17.4%).

The prevalence of BMI was highest in patients with lymphoplasmacytic lymphoma at 92.3%, followed by Burkitt lymphoma at 75.0% and mantle cell lymphoma at 73.3%.

Percentage of involvement

Of the 260 cases with bone marrow involvement, there were 157 males and 103 females (1.5:1 M:F ratio) with the mean age of 59 years, the median age of 61.5 years, and range from 16 to 90 years.

The percentage of bone marrow involvement

Table 2. Prevalence of bone marrow involvement in lymphoma

Lymphoma type	Prevalence; n (%)	Prevalence of BMI; n (%)
B-cell non-Hodgkin lymphoma	902 (83.2)	239/902 (26.5)
Lymphoplasmacytic lymphoma	13 (1.2)	12/13 (92.3)
Burkitt lymphoma	12 (1.1)	9/12 (75.0)
Mantle cell lymphoma	30 (2.7)	22/30 (73.3)
B-cell non-Hodgkin lymphoma	17 (1.5)	12/17 (70.6)
Small lymphocytic lymphoma	4 (0.4)	2/4 (50.0)
High-grade B-cell lymphoma, NOS	14 (1.3)	6/14 (42.9)
Follicular lymphoma	28 (2.6)	10/28 (35.7)
Marginal zone lymphoma	158 (14.6)	44/158 (27.8)
DLBCL, NOS	621 (57.3)	122/621 (19.6)
THRLBCL	5 (0.5)	0/5 (0.0)
T-cell non-Hodgkin lymphoma	112 (10.4)	16/112 (14.3)
Peripheral T-cell lymphoma, NOS	41 (3.8)	11/41 (29.3)
Mycosis fungoides	4 (0.4)	1/4 (25.0)
AITL	7 (0.6)	1/7 (14.3)
Anaplastic large cell lymphoma	29 (2.7)	2/29 (6.9)
Extranodal NK/T cell lymphoma	21 (1.9)	0/21 (0.0)
SPTCL	6 (0.6)	0/6 (0.0)
Intestinal T-cell lymphoma	2 (0.2)	0/2 (0.0)
MEITL	1 (0.1)	0/1 (0.0)
Hepatosplenic T-cell lymphoma	1 (0.1)	0/1 (0.0)
Hodgkin lymphoma	69 (6.4)	12/69 (17.4)
Classical Hodgkin lymphoma	65 (6.0)	12/65 (18.5)
NLPHL	4 (0.4)	0/4 (0.0)

AITL=angioimmunoblastic T-cell lymphoma; DLBCL=diffuse large B-cell lymphoma; MEITL=monomorphic epitheliotropic intestinal T-cell lymphoma; NLPHL=nodular lymphocyte-predominant Hodgkin lymphoma; NOS=not otherwise specified; SPTCL=subcutaneous panniculitis-like T-cell lymphoma; THRLBCL=T-cell/histiocyte-rich large B-cell lymphoma

Table 3. Percentage of bone marrow involvement

Lymphoma type	n	% marrow involvement; median (range)
B-cell non-Hodgkin lymphoma	234	
Diffuse large B-cell lymphoma	121	30 (5 to 100)
Burkitt lymphoma	9	90 (10 to 95)
High-grade B-cell lymphoma, NOS	6	30 (5 to 90)
Follicular lymphoma	10	25 (5 to 95)
Marginal zone lymphoma	43	10 (1 to 90)
Small lymphocytic lymphoma	2	60 (20 to 99)
Mantle cell lymphoma	20	20 (5 to 95)
Lymphoplasmacytic lymphoma	11	30 (10 to 95)
B-cell non-Hodgkin lymphoma	12	20 (5 to 95)
T-cell non-Hodgkin lymphoma	14	
Angioimmunoblastic T-cell lymphoma	1	40 (-)
Anaplastic large cell lymphoma	2	20 (10 to 30)
Peripheral T-cell lymphoma, NOS	11	60 (5 to 90)
Hodgkin lymphoma	12	
Classical Hodgkin lymphoma	12	85 (30 to 99)

NOS=not otherwise specified

of B-cell NHL (Table 3) was highest in Burkitt lymphoma and SLL. Marginal zone lymphoma (MZL) showed the lowest percentage of involvement. The percentage of bone marrow involvement of T-cell NHL revealed PTCL, NOS had a similar percentage of involvement to the other types. For HL, it had the great degree of involvement at the mean and median percentages of 71 and 85, respectively.

Patterns

The most common pattern was an interstitial pattern at 32.7%, while the least common pattern was an intrasinusoidal pattern at 2.0%. The primary pattern of BMI in NHL is illustrated in Figure 2 and summarized in Table 4.

A diffuse pattern was most common in DLBCL and Burkitt lymphoma. An interstitial pattern was found in high-grade B-cell lymphoma, MZL, mantle cell lymphoma, and all subtypes of T-cell lymphoma. This pattern was absent in follicular lymphoma and SLL. An intrasinusoidal pattern was present in DLBCL and extranodal MZL. A mixed pattern was most common in lymphoplasmacytic lymphoma. A nodular pattern was present in DLBCL, MZL, and B-cell NHL. A paratrabecular pattern was most common in follicular lymphoma. It was also found in DLBCL, MZL, mantle cell lymphoma, and lymphoplasmacytic lymphoma.

The patterns of BMI in HL are illustrated in Figure 3. RS cells could be identified in 10/12 cases (83.3%). The characteristic background of bone marrow in the involved cases consisted of fibrosis, mixed inflammatory cells, or granuloma. Only the characteristic background without RS cells was present in 2/12 (16.7%).

Discordance

The discordant lymphoma was referred to two or more distinct histologic subtypes occurring in different anatomical sites. In the present study, a discordant histology between bone marrow and primary anatomic site was found in DLBCL at 12.4% (15/121) cases and MZL at 2.3% (1/44) cases.

With Stata version 16.1, the authors found that patients with both groups of discordant and concordant DLBCL had a relapsed disease (Figure 4). However, patients with discordant DLBCL tended to live longer than patients with concordant DLBCL (Figure 5). In particular, there was only one case

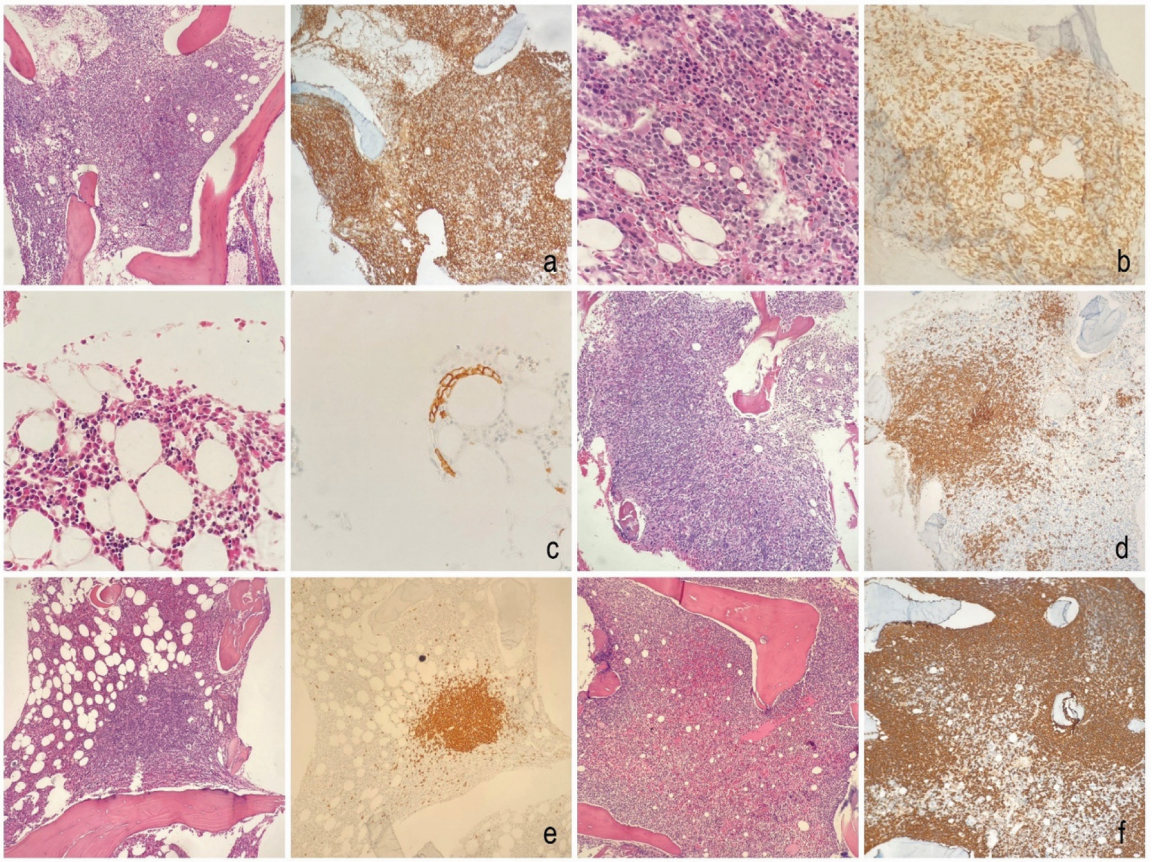

Figure 2. Patterns of bone marrow involvement per H&E and immunostaining (CD20). (a) Diffuse pattern. (b) Interstitial pattern. (c) Intrasinusoidal pattern. (d) Mixed pattern, nodular, and interstitial. (e) Nodular pattern. (f) Paratrabecular pattern.

Table 4. Patterns of bone marrow involvement in non-Hodgkin lymphoma

Lymphoma type	Primary pattern					
	Diffuse	Interstitial	Intrasinusoidal	Mixed	Nodular	Paratrabecular
DLBCL (121)	40	40	4	19	8	10
BL (9)	6	3	0	0	0	0
HGBL, NOS (6)	2	3	0	1	0	0
FL (10)	1	0	0	3	0	6
MZL (43)	8	11	1	10	10	3
Extranodal (26)	4	7	1	5	7	2
Nodal (12)	3	4	0	2	2	1
Splenic (5)	1	0	0	3	1	0
SLL (2)	1	0	0	1	0	0
MCL (20)	7	8	0	2	1	2
LPL (11)	1	3	0	5	0	2
B-cell NHL (12)	4	3	0	4	1	0
AITL (1)	0	1	0	0	0	0
ALCL (2)	0	2	0	0	0	0
PTCL, NOS (11)	4	7	0	0	0	0
Total (260)	74 (29.8%)	81 (32.7%)	5 (2.0%)	45 (18.1%)	20 (8.1%)	23 (9.3%)

AITL=angioimmunoblastic T-cell lymphoma; ALCL=anaplastic large cell lymphoma; BL=Burkitt lymphoma; DLBCL=diffuse large B-cell lymphoma; FL=follicular lymphoma; HGBL=high-grade B-cell lymphoma; LPL=lymphoplasmacytic lymphoma; MCL=mantle cell lymphoma; MZL=marginal zone lymphoma; NHL=non-Hodgkin lymphoma; NOS=not otherwise specified; PTCL=peripheral T-cell lymphoma; SLL=small lymphocytic lymphoma

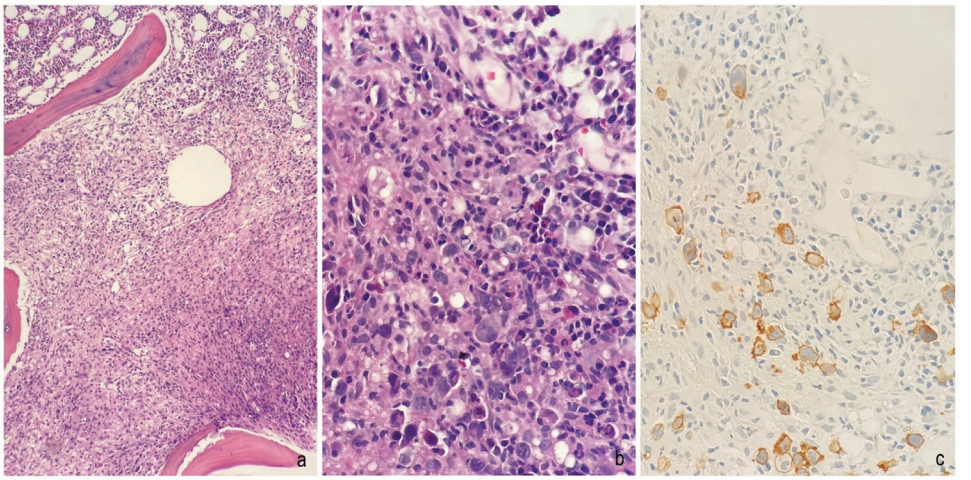

Figure 3. Patterns of bone marrow involvement in HL. (a) Background of fibrosis and mixed inflammatory pattern. (b) Reed-Sternberg cells among mixed inflammatory background. (c) Reed-Sternberg cells a re highlighted by CD30.

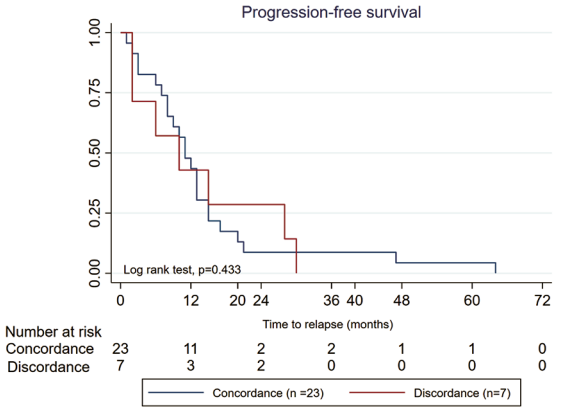

Figure 4. The Kaplan-Meier estimates curves showed progression-free survival for groups of patients with discordant and concordant diffuse large B-cell lymphoma.

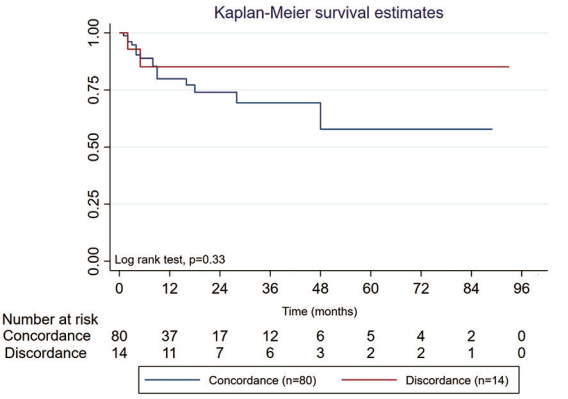

Figure 5. The Kaplan-Meier estimates curves showed overall survival for groups of patients with discordant and concordant diffuse large B-cell lymphoma.

of patient with discordant MZL. This patient had a relapsed disease and a 19-month follow-up duration with alive vital status at the last follow-up. With only one case of discordant MZL, the authors could not compare it with the concordant cases.

Discussion

The prevalence of lymphoma in Thailand is different from Western countries[9,10]. The most common subtype in Thailand was DLBCL followed by FL and MZL reported by Intragumtornchai et al (2018)[9]. The present study had fewer populations with the majority from the Northern part of Thailand. The three leading subtypes were DLBCL, MZL, and MCL. For Western countries, the most frequent subtypes were DLBCL, CLL/SLL, and FL. The different prevalence of the disease could affect the prevalence of BMI in the different regions.

The prevalence of BMI in NHL was higher than HL, and B-cell NHL was higher than T-cell NHL. However, it was different from the work found by Kumar et al (2009) in India showing T-cell NHL with a higher prevalence of BMI than B-cell NHL[11]. In the present study, there were more cases with B-cell NHL than cases with T-cell NHL. The prevalence of BMI in HL was close to a previous study by Viswanatha and Foucar (2003) with the reservation of no representative cases from NLPHL was in the present study[3].

The prevalence of BMI of each subtype is surprisingly contrasting. The present study findings revealed that LPL was the most common B-cell NHL

to involve the bone marrow while another study[1] in Thailand showed that MCL was the one. Nonetheless, the cases with LPL were quite limited.

A diffuse pattern of BMI was common in DLBCL and BL, which correlated with a high percentage of involvement. Both had an aggressive course, but this pattern was also found in low-grade B-cell lymphoma such as MZL. The interstitial pattern was non-specific, and it could be present in any subtypes of lymphoma. Only FL and SLL did not have an interstitial pattern of involvement. Few cases had an intrasinusoidal pattern that was present in DLBCL and extranodal MZL. This pattern was difficult to evaluate and better confirmed by immunohistochemical stains. In addition, it could be missed due to other easily identified predominant patterns and a loss from deeper levels. LPL in bone marrow mostly had a mixed pattern, however, other B-cell lymphoma subtypes could be present with a mixed pattern of involvement. A nodular pattern was the second least common pattern of BMI. It was found in DLBCL, MZL, and MCL. Finally, a paratrabecular pattern was most common in FL and found in other subtypes.

In the present study, the mixed pattern in FL also contained a paratrabecular pattern as well. According to the result, the authors should raise the suspicion of FL in cases with paratrabecular involvement. However, the other subtypes of lymphoma could be present with this pattern.

There were only five cases of splenic MZL and none of them had an intrasinusoidal pattern. This was not sufficient to support the result of a characteristic feature in splenic MZL in the other studies[12].

Cases in the B-cell NHL category included patients that denied further investigation or died before further management. The information that could be provided from this group was only for the B-cell subtype.

BMI in HL mostly presented with RS cells in the background of mixed inflammatory cells, granuloma, or fibrosis. These background findings were a characteristic feature of HL resulting from overexpression of cytokine/chemokine[5]. Two cases that had only a characteristic background were considered to have an involvement. Therefore, the presentation of mixed inflammatory cells and granuloma in bone marrow biopsy should not only look for microorganisms but also carefully look for RS cells and correlate with the clinical history.

The studies of discordant lymphoma were limited and the prevalence had a range from between 5% and 24%[2]. In the present study, the discordant DLBCL was 12.4%. Although both groups of discordant and concordant DLBCL had a relapsed disease, patients with discordant DLBCL tended to live longer. As a result, discordance is one of the important indicators to be identified because the treatment of the discordant and concordant cases in the future might be different.

Conclusion

Each subtype of lymphoma has different prevalence and tends to involve marrow in the dissimilar ways. It is important to evaluate the morphology of marrow, especially when it comes to lymphoma staging. In particular, specific lymphomas have a preference in the pattern of BMI, so that pattern recognition of BMI could give the clue to differential diagnosis. Immunohistochemistry helps support the diagnosis, especially in intrasinusoidal pattern and cases with minimal involvement, which are hard to assess from the morphology alone. The discordant DLBCL tends to have a better prognosis, and the present study finding might affect the treatment in the future. For these reasons, careful and correct diagnosis is required for proper patient management.

What is already known on this topic?

Lymphomas have a pattern preference in bone marrow involvement. However, studies on the pattern of BMI show different results across the regions. In studies, patients with concordant lymphoma have inferior overall survival compared to those with discordant one.

What this study adds?

The detection of patterns of bone marrow involvement could give the differential diagnosis of the subtypes of lymphoma. The discordant diffuse large B-cell lymphoma tends to have a better prognosis, and this finding might affect the treatment in the future.

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Conflicts of interest

The authors declare no conflict of interest.

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