

Original Article

Pathologic Findings before Diagnosing Malignant Lymphoma – a Retrospective Study in a Large Medical Institute

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Abstract:

Introduction: Information regarding pathologic findings before diagnosing malignant lymphoma is lacking.

Objective: To gather information especially pathology findings from patients with lymphoma seen at a large medical institute. **Methods:** A laboratory information system was used to retrieve patients with lymphoma patients that received first diagnosis or had pathologic samples during follow-up in 2016 at Siriraj Hospital including in-/outpatients and consultation cases. Then all the pathologic samples were reviewed to confirm the diagnosis and subtyping of lymphoma according to the WHO classification (revised 4th edition, 2017). Moreover, any clinical information or pathologic findings related to lymphoma were searched for. **Results:** Overall 999 patients with lymphoma were seen in 2016, including Hodgkin's lymphoma, 72 cases (7.2%), B-cell lymphoma, 794 cases (79.5%) and T & NK-cell lymphoma, 133 cases (13.3%). The demographic data and subtypes of lymphoma were comparable to related lymphoma studies. Interesting clinical information other than common clinical features of lymphoma were found in 97 cases (9.7%) including chronic infections (33 cases), previously treated hematologic diseases (21 cases), cancers and precancerous lesions (18 cases), autoimmune disorders, allergies, or chronic skin diseases (11 cases), chronic inflammation or ulcers (9 cases) and benign tumor, hyperplasia, or cystic lesion (7 cases). Interesting pathologic findings included accompanying lymphoma (33 cases), associated infections (54 cases), incorrect subtyping of lymphoma (20 cases), preceding lymphoproliferative disorders (20 cases), failure to recognize lymphoma for a period of time before a definite diagnosis of lymphoma (13 cases), histologic transformation (44 cases) and second malignancy (5 cases). **Conclusion:** The pathologic findings before diagnosing malignant lymphoma raise the concern to develop practice guidelines to prevent misdiagnosis.

Keywords : ● Lymphoma ● Associated conditions ● Lymphoproliferative disorders ● Transformation
● Misdiagnosis

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นิพนธ์ต้นฉบับ

สิ่งตรวจพบทางพยาธิวิทยาก่อนได้รับการวินิจฉัยเป็นมะเร็งต่อมน้ำเหลือง – การศึกษาย้อนหลังในสถาบันการแพทย์ขนาดใหญ่แห่งหนึ่ง

สัญญา สุขพนิชนันท์

ภาควิชาพยาธิวิทยา คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล

บทคัดย่อ

ที่มา ข้อมูลสิ่งตรวจพบทางพยาธิวิทยาก่อนได้รับการวินิจฉัยเป็นมะเร็งต่อมน้ำเหลืองยังมีน้อย **วัตถุประสงค์** เพื่อรวบรวมข้อมูลสิ่งตรวจพบทางพยาธิวิทยาจากผู้ป่วยมะเร็งต่อมน้ำเหลืองที่ได้รับการดูแลรักษาในสถาบันการแพทย์ขนาดใหญ่แห่งหนึ่ง **วิธีการวิจัย** ใช้ระบบข้อมูลห้องปฏิบัติการในการดึงข้อมูลผู้ป่วยมะเร็งต่อมน้ำเหลืองที่ได้รับการวินิจฉัยครั้งแรกหรือมีสิ่งส่งตรวจระหว่างการจัดติดตามในปี พ.ศ. 2559 ที่โรงพยาบาลศิริราช โดยรวมผู้ป่วยในและนอกตลอดจนผู้ป่วยที่อื่นที่ส่งเข้ามาขอรับการปรึกษาทางพยาธิวิทยา จากนั้นตรวจสอบสิ่งส่งตรวจทางพยาธิวิทยาทั้งหมดเพื่อยืนยันการวินิจฉัยและการจำแนกชนิดของมะเร็งต่อมน้ำเหลืองตามการจำแนกประเภทโดยองค์การอนามัยโลก (ครั้งที่ 4 ฉบับปรับปรุง, ค.ศ. 2017) นอกจากนี้ ยังค้นหาข้อมูลทางคลินิกหรือสิ่งตรวจพบทางพยาธิวิทยาที่เกี่ยวข้องกับมะเร็งต่อมน้ำเหลืองด้วย **ผลการศึกษา** พบผู้ป่วยมะเร็งต่อมน้ำเหลืองทั้งหมด 999 คนในปี พ.ศ. 2559 เป็นชนิดฮอดจ์กิน 72 ราย (ร้อยละ 7.2) ชนิดบี-เซลล์ 794 ราย (ร้อยละ 79.5) และชนิดที- และเอ็นเค-เซลล์ 133 ราย (ร้อยละ 13.3) ข้อมูลทางประชากรศาสตร์และชนิดย่อยของมะเร็งต่อมน้ำเหลืองเปรียบเทียบได้ไม่แตกต่างจากการศึกษามะเร็งต่อมน้ำเหลืองก่อนหน้านี้ พบข้อมูลทางคลินิกที่น่าสนใจนอกเหนือจากที่พบบ่อยในมะเร็งต่อมน้ำเหลือง 97 ราย (ร้อยละ 9.7) ได้แก่ การติดเชื้อเรื้อรัง (33 ราย) โรคเลือดที่รักษามาแล้ว (21 ราย) มะเร็งและรอยโรคก่อนเป็นมะเร็ง (18 ราย) โรคภูมิคุ้มกันตนเอง ภูมิแพ้ หรือโรคผิวหนังเรื้อรัง (11 ราย) การอักเสบหรือแผลเรื้อรัง (9 ราย) และเนื้องอกไม่ร้าย การเจริญเกิน หรือรอยโรคถุงน้ำ (7 ราย) สำหรับสิ่งตรวจพบทางพยาธิวิทยาที่น่าสนใจ ได้แก่ มะเร็งต่อมน้ำเหลืองอีกชนิดที่พบร่วม (33 ราย) การติดเชื้อร่วม (54 ราย) การวินิจฉัยชนิดย่อยของมะเร็งต่อมน้ำเหลืองไม่ถูกต้อง (20 ราย) การเพิ่มเซลล์ลิมโฟไซต์ผิดปกติที่เกิดขึ้นก่อนหน้า (20 ราย) ความล้มเหลวในการนึกถึงมะเร็งต่อมน้ำเหลืองเป็นระยะเวลาหนึ่งก่อนหน้าการวินิจฉัยได้ (13 ราย) การแปรูปทางกล้องจุลทรรศน์ (44 ราย) และมะเร็งชนิดที่ 2 (5 ราย) **สรุป** สิ่งตรวจพบทางพยาธิวิทยาก่อนการวินิจฉัยเป็นมะเร็งต่อมน้ำเหลืองยกประเด็นให้พิจารณาเรื่องการพัฒนาแนวทางปฏิบัติเพื่อป้องกันการวินิจฉัยผิด

คำสำคัญ : ● Lymphoma ● Associated conditions ● Lymphoproliferative disorders ● Transformation
● Misdiagnosis

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต 2561;28:165-77.

Introduction

Various types of lymphoma studies are commonly found in the literature concerning etiologies, tumor behavior, diagnosis, classification, prognostic index, treatments and clinical outcomes. Recently, incipient or low-risk lesions have been proposed in the WHO classification (revised 4th edition, 2017), including monoclonal B-cell lymphocytosis, monoclonal gammopathy of undetermined significance (MGUS) of IgM, IgG or IgA, monoclonal immunoglobulin deposition diseases, in situ follicular neoplasia, in situ mantle cell neoplasia, EBV+ mucocutaneous ulcer, chronic lymphoproliferative disorder (LPD) of NK cells, hydroa vacciniforme-like LPD, indolent T-cell LPD of the GI tract, primary cutaneous CD30+ T-cell LPDs (in particular lymphomatoid papulosis), primary cutaneous CD4+ small to medium T-cell LPD, and breast implant-associated anaplastic large cell lymphoma.¹ Moreover, chronic infections, autoimmune disorders, immunodeficiency states, drug reactions, chemical exposure and other conditions have been suspected as risk or predisposing factors in lymphomagenesis.²⁻¹² Nevertheless, information regarding pathologic findings before diagnosing malignant lymphoma is still lacking.

The objective of this study was to gather information especially pathologic findings from patients with lymphoma seen at a large medical institute where approximately 200 to 250 new cases of lymphoma have been diagnosed each year^{13,14} as well as a large number of follow-up and consultation cases. Then interesting pathologic findings may lead to improved daily pathology practice.

Materials and Methods

A laboratory information system with available pathologic data and clinical information in requisition since October 2006 was used to retrieve information on patients with lymphoma receiving a first diagnosis or having pathologic samples during follow-up in 2016 at Siriraj Hospital including in- and outpatients and con-

sultation cases. Then all pathologic samples submitted from each patient were reviewed to confirm the diagnosis and subtyping of lymphoma according to the WHO classification (revised 4th edition, 2017).¹ Moreover, the clinical information given in the requisition at each submission of pathologic samples was collected, especially when the clinical information was beyond the common clinical features of lymphoma. Then a review of these pathologic samples before diagnosing lymphoma was performed to find pathologic findings related to lymphoma.

Before conducting this study, a research proposal was submitted to the Siriraj Institutional Review Board (SIRB) to consider the ethical issues on research involving human subjects. The certificate of approval was granted November 17, 2016 (Si 736/2016) so the study could commence and be carried out within one year.

Results

From the laboratory information system at Siriraj Hospital Pathology Laboratory between 1 January 2016 and 31 December 2016, 999 cases were diagnosed as malignant lymphoma. All available materials in these cases were reviewed.

Demographic data

The patient age ranged from 2 to 91 years (mean, 55.5 years; median, 58 years). Male to female ratio was 1.1 (532 males and 467 females) totaling 974 Thais (97.4%) and 25 foreigners (2.5%). The number of patients belonging to Siriraj Hospital was 550 (55.1%); 390 (71%) were newly diagnosed while the other 160 cases (29%) were known cases of lymphoma during follow-up visits and providing samples for pathologic examination. The remaining 449 patients were consultation cases (44.9%); 426 (94.9%) were newly diagnosed while the other 23 cases (5.1%) were known cases of lymphoma during follow-up visits at other hospitals but providing samples for pathologic examination submitted for consultation at Siriraj Hospital that has been one of the limited number of hematopathology consultation services in Thailand since 1993.

Types of malignant lymphoma

The 999 cases of malignant lymphoma were reviewed. As already mentioned, they included newly diagnosed and follow-up cases in 2016. The slides were retrieved for review and comprised 72 cases of Hodgkin's lymphoma (7.2%) and 927 cases of non Hodgkin's lymphoma (NHL) (92.8%). Among the cases of Hodgkin's lymphoma, 4 cases were nodular lymphocyte predominant Hodgkin's lymphoma (0.4% of all lymphomas or 5.6% of Hodgkin's lymphoma) and 68 cases were classical Hodgkin's lymphoma (6.8% of all lymphomas & 94.4% of Hodgkin's lymphoma). Among the NHL, 794 cases were B-cell lymphoma (79.5% of all lymphomas or 85.7% of all NHLs) and 133 cases were T- & NK-cell lymphomas (13.3% of all lymphomas & 14.3% of all NHLs). Each case of malignant lymphoma was diagnosed according to the WHO classification (revised 4th edition, 2017)¹ as shown in Table 1.

Pathologic findings prior to the diagnosis of malignant lymphoma

Among the 999 cases, using the laboratory information system, all previous materials in each case along with clinical information given in the requisition at each time were retrieved for review to find any LPD or any overlooked lymphoma. In all, 97 cases (9.7%) exhibited clinical history regarding chronic infections, previously treated hematologic malignancy, MGUS, cancers and precancerous lesions (nonhematologic), autoimmune disorders, allergy, chronic skin diseases, chronic inflammation, ulcer, benign tumor, hyperplasia, or cystic lesion (leading to previous surgical operation or biopsy) (Table 2).

During the review of pathologic samples available in each case, interesting pathologic results were found in terms of accompanying lymphoma, associated infection, incorrect subtyping of lymphoma, failure to recognize lymphoma, preceding lymphoproliferative lesions, or monoclonal lymphoid proliferation, histologic transformation and second malignancy. (Table 3)

Discussion

Notably, clinical information making a definite diagnosis of the lymphoma type is important because in follow-up cases, the information given in the requisition can confirm primary lymphoma at extranodal sites or some specific types of lymphoma such as splenic MZL, nodal MZL, LPL, primary cutaneous follicle center lymphoma, primary DLBCL of the CNS, primary mediastinal large B-cell lymphoma, intravascular large B-cell lymphoma, systemic EBV+ T-cell lymphoma of childhood, primary cutaneous ALCL, primary cutaneous gamma-delta T-cell lymphoma and primary cutaneous CD4+ small/medium T-cell LPD.

The frequency of lymphoma types in this study, despite the fact that the patients were newly diagnosed or during follow-up visits, is comparable to those reported from Thailand using the WHO classification.^{14,15} Some types, however, were higher than those reported from the whole country, possibly due to the higher opportunity to obtain pathology samples for diagnosis depending on the available procedures and surgical operations, for example, primary DLBCL of the CNS. Siriraj Hospital is the largest hospital in Thailand with 2,000 inpatient beds and more than 3 million outpatient visits.

Regarding previous clinical history other than common clinical features of lymphoma that could be gathered from the requisition in 97 cases (9.7%), included chronic infections (33 cases), previously treated hematologic diseases (21 cases), cancers and precancerous lesions (18 cases), autoimmune disorders, allergy, or chronic skin diseases (11 cases), chronic inflammation or ulcers (9 cases), and benign tumor, hyperplasia, or cystic lesion (7 cases). It looks like not many lymphoma patients (only 9.7%) have previous clinical history that may or may not be related to lymphoma. Nevertheless, some clinical information is important and should serve as a warning or area of concern regarding the possibility of lymphoma or, on the contrary, avoiding over diagnosis of lymphoma. Chronic infections, autoimmune disorders, allergy, chronic skin diseases, chronic inflam-

Table 1 Types of 999 cases of non Hodgkin's lymphomas diagnosed and followed up in 2016 at Siriraj Hospital**Hodgkin's lymphoma (72 cases)**

Nodular lymphocyte predominant Hodgkin's lymphoma (nLPHL) (4 cases)

Classical Hodgkin's lymphoma (CHL) (68 cases) including nodular sclerosis, 37 cases (54.4%), mixed cellularity, 9 cases (13.2%), lymphocyte-rich, 3 cases (4.4%), lymphocyte-depleted, 4 cases (5.9%), and unable to subtype (due to small sample size), 15 cases (22.1%)

B-cell lymphomas (794 cases)

Diffuse large B-cell lymphoma (DLBCL), 411 cases (41.1% of all lymphomas or 51.8% of all B-cell lymphomas), 32 cases (7.8% of DLBCL) with accompanying lymphomas including follicular lymphoma, 17 cases (53.1%), extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma), 8 cases and marginal zone lymphoma (MZL), 1 case, total of 9 cases (28.1%), small lymphocytic lymphoma (SLL), 3 cases (9.4%), small B-cell lymphoid neoplasm (SBCLN), 1 case (3.1%), lymphoplasmacytic lymphoma (LPL), 1 case (3.1%) and angioimmunoblastic T-cell lymphoma (AITL), 1 case (3.1%). (Note: excluding these DLBCL with accompanying lymphomas in their corresponding ones for avoiding confusion upon calculation)

All MZL case totaled 130 cases (13.0% of all lymphomas or 16.4% of all B-cell lymphomas), including MZL, 77 cases (excluding MALT lymphoma of the GI tract, nodal MZL and splenic MZL), GI MALT lymphoma, 18 cases, nodal MZL, 23 cases and splenic MZL, 12 cases (Note: excluding the 9 cases accompanied with DLBCL)

Follicular lymphoma (FL) 62 cases (6.2% of all lymphomas or 7.8% of all B-cell lymphomas) (Note: excluding the 17 cases accompanied with DLBCL)

Mantle cell lymphoma (MCL), 38 cases (3.8% of all lymphomas or 4.8% of all B-cell lymphomas)

Primary DLBCL of the central nervous system (CNS), 32 cases (3.2% of all lymphomas or 4.0% of all B-cell lymphomas)

Burkitt lymphoma (BL), 28 cases (2.8% of all lymphomas or 3.5% of all B-cell lymphomas)

LPL, 22 cases (2.2% of all lymphomas or 2.8% of all B-cell lymphomas) (Note: excluding 1 case accompanied with DLBCL)

Primary mediastinal large B-cell lymphoma (PMBL), 15 cases (1.5% of all lymphomas or 1.9% of all B-cell lymphomas)

SLL, 15 cases (excluding cases first presented with chronic lymphocytic leukemia, CLL) (1.5% of all lymphomas or 1.9% of all B-cell lymphomas) (Note: excluding the 3 cases accompanied with DLBCL)

Plasmablastic lymphoma (PBL), 11 cases (1.1% of all lymphomas or 1.4% of all B-cell lymphomas)

High-grade B-cell lymphoma (HGBL), 10 cases (9 cases between DLBCL and BL and 1 case with blastoid feature but *MYC* gene rearrangement) (1.0% of all lymphomas or 1.3% of all B-cell lymphomas)

SBCLN, 9 cases (no further immunostaining performed to classify) (0.9% of all lymphomas or 1.1% of all B-cell lymphomas) (Note: excluding the 1 case accompanied with DLBCL)

Intravascular large B-cell lymphoma (IVBL), 8 cases (0.8% of all lymphomas or 1.0% of all B-cell lymphomas)

Primary cutaneous follicle center lymphoma (PCFL), 1 case (0.1% of all lymphomas or 0.1% of all B-cell lymphomas)

Table 1 Types of 999 cases of non Hodgkin's lymphomas diagnosed and followed up in 2016 at Siriraj Hospital (continued)

B lymphoblastic lymphoma (B-LBL), 1 case (excluding case with acute B lymphoblastic leukemia at marrow staging) (0.1% of all lymphomas or 0.1% of all B-cell lymphomas)

Unclassifiable B-cell lymphoma with features intermediate between DLBCL and CHL, 1 case (0.1% of all lymphomas or 0.1% of all B-cell lymphomas)

T- & NK-cell lymphomas (133 cases)

Peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS), 31 cases (3.1% of all lymphomas or 23.3% of all T- & NK-cell lymphomas)

NK/T-cell lymphoma, nasal type, 25 cases (nasal site and surrounding, 21 cases and extra-nasal site, 4 cases) (2.5% of all lymphomas or 18.8% of all T- & NK -cell lymphomas)

AITL, 23 cases (2.3% of all lymphomas or 17.3% of all T- & NK -cell lymphomas) (Note: excluding 1 case accompanied with DLBCL)

T lymphoblastic lymphoma (T-LBL), 8 cases (excluding case with acute T lymphoblastic leukemia at marrow staging) (0.8% of all lymphomas or 6.0% of all T- & NK -cell lymphomas)

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL), 8 cases (0.8% of all lymphomas or 6.0% of all T- & NK -cell lymphomas)

Mycosis fungoides (MF), 7 cases (0.7% of all lymphomas or 5.3% of all T- & NK -cell lymphomas)

ALK+ anaplastic large cell lymphoma (ALCL), 7 cases (0.7% of all lymphomas or 5.3% of all T- & NK -cell lymphomas)

Primary cutaneous ALCL, 7 cases (0.7% of all lymphomas or 5.3% of all T- & NK -cell lymphomas)

ALK-negative ALCL, 6 cases (0.7% of all lymphomas or 4.5% of all T- & NK -cell lymphomas)

Primary cutaneous gamma-delta T-cell lymphoma, 4 cases (0.4% of all lymphomas or 3.0% of all T- & NK -cell lymphomas)

Primary cutaneous CD4+ small/medium T-cell LPD, 2 cases (0.2% of all lymphomas or 1.5% of all T- & NK -cell lymphomas)

Aggressive NK cell leukemia, 1 case (0.1 % of all lymphomas or 0.8% of all T- & NK -cell lymphomas)

NK cell neoplasm, 1 case (hepatosplenomegaly with hemophagocytic syndrome) (0.1 % of all lymphomas or 0.8% of all T- & NK -cell lymphomas)

Nodal PTCL with T follicular helper phenotype, 1 case (0.1 % of all lymphomas or 0.8% of all T- & NK -cell lymphomas)

EBV-associated T-cell lymphoma of childhood, 1 case (0.1 % of all lymphomas or 0.8% of all T- & NK -cell lymphomas)

Monomorphic epitheliotropic intestinal T-cell lymphoma (enteropathy-associated T-cell lymphoma, type II), 1 case (0.1 % of all lymphomas or 0.8% of all T- & NK -cell lymphomas)

Table 2 Categories of clinical history in 97 cases*

Chronic infections, 33 cases, including HIV infection, 24 cases, tuberculosis, 3 cases, HBV, 2 cases (one with cirrhosis), HCV, 2 cases (one with cirrhosis), chronic EBV infection, 1 case and pulmonary nocardiosis, 1 case
Previously treated lymphomas, leukemia, and MGUS, 21 cases including DLBCL, 4 cases, follicular lymphoma, 4 cases, lymphoma (type not known), 3 cases, MALT lymphoma, 3 cases, SLL/CLL, 1 case, primary cutaneous follicle center lymphoma, 1 case, primary cutaneous CD30+ LPD, 1 case, acute myeloid leukemia, 1 case and MGUS, 3 cases
Cancers (nonhematologic) and precancerous lesion, 18 cases, including CA prostate, 3 cases, pulmonary adenocarcinoma, 2 cases, hepatocellular carcinoma, 2 cases, CA uterine cervix, 2 cases, adenocarcinoma of gallbladder, 1 case, CA vulva, 1 case, CA breast, 1 case, CA colon, 1 case, papillary thyroid carcinoma, 1 case, metastatic adenocarcinoma, 1 case, metastatic nonsmall cell carcinoma, 1 case, ductal carcinoma in situ, 1 case and extra-mammary Paget disease, 1 case
Autoimmune disorders, allergy, or chronic skin diseases, 11 cases including SLE, 2 cases, rheumatoid arthritis, 1 case, Hashimoto thyroiditis, 1 case, Sjögren syndrome, 1 case, AIHA, 1 case, atopic dermatitis, 2 cases, psoriasis, 2 cases and bullous pemphigoid, 1 case
Chronic inflammation or ulcers, 9 cases including cirrhosis, 3 cases (one with HBV, another with HCV and the other with chronic kidney disease), chronic cholecystitis, 2 cases, chronic meningitis, 1 case, chronic inflammation of the lacrimal gland, 1 case, chronic oral ulcer, 1 case and chronic ulcer at the nasal septum, 1 case
Benign tumor, hyperplasia, or cystic lesion, 7 cases including mucinous cystadenoma of the ovary, 1 case, phylloides tumor, 1 case, gastric schwannoma, 1 case, colonic schwannoma, 1 case, prostatic nodular hyperplasia, 2 cases and benign multiloculated cyst of the neck, 1 case

*2 cases had comorbidity - one with HBV cirrhosis and the other with HCV cirrhosis

Table 3 Interesting pathologic findings found during review

Accompanying lymphoma (33 cases)

32 cases of DLBCL were found to have accompanying lymphoma in the same histologic sections or in the marrow staging, including FL, 17 cases, MALT lymphoma, 8 cases, SLL, 3 cases, MZL, 1 case, LPL, 1 case, SBCLN, 1 case and AITL, 1 case.

One case of FL was found to have Langerhans cell sarcoma (LCS) within the same lymph node (Note: this particular case is also considered to have morphologic transformation because FL was first diagnosed 5 years ago, then the groin lymph node enlargement in 2016 was found to have both FL and LCS.)

Associated infection (54 cases)

EBV infection detected by in situ hybridization for EBV-encoded small RNA (EBER), 48 cases including CHL, 3 cases, B-cell lymphoma, 3 cases (DLBCL, 2 cases, HGCL, 1 case) and T-cell lymphoma, 42 cases including extranodal NK/T-cell lymphoma, 24 cases (nasal, 21 cases and extranasal, 3 cases), AITL, 15 cases, systemic EBV+ T-cell lymphoma of childhood, 1 case, aggressive NK cell leukemia, 1 case and NK cell neoplasm, 1 case

Helicobacter pylori 6 cases (4 in MALT lymphoma and 2 in DLBCL of stomach)

Table 3 Interesting pathologic findings found during review (continued)**Incorrect subtyping of lymphoma (20 cases)**

One case of AITL was incorrectly subtyped as MZL.

One case of ALK+ ALCL was incorrectly subtyped as nodular sclerosis CHL.

One case of BL was incorrectly subtyped as DLBCL.

Four cases of CHL were incorrectly subtyped as ALCL, 2 cases, DLBCL, 1 case and diffuse large cell lymphoma (by morphology alone), 1 case.

Four cases of DLBCL were incorrectly subtyped as CHL, 1 case, FL grade, 3/3 1 case, ALCL, 1 case and AITL, 1 case.

One case of HGBL was incorrectly subtyped as SBCLN.

Two cases of MCL were both incorrectly subtyped as FL.

One case of extranodal NK/T-cell lymphoma was incorrectly subtyped as ALCL.

One case of nLPHL was incorrectly subtyped as SLL/CLL.

One case of nodal MZL was incorrectly subtyped as Hodgkin lymphoma (by morphology alone).

One case of SBCLN was incorrectly subtyped as DLBCL.

One case of SLL was incorrectly subtyped as MZL.

One case of splenic MZL was incorrectly subtyped as CLL.

Preceding lymphoproliferative disorders (20 cases)

One case of atypical lymphoid hyperplasia of the lymph node 2 years before the definite diagnosis of DLBCL

One case of bronchus-associated lymphoid tissue with chronic inflammation 1 year ago (2 biopsies) before the definite diagnosis of pulmonary MZL

Three cases of primary cutaneous CD30+ LPDs (one case up to 6 years) before the definite diagnosis of primary cutaneous ALCL

One case of chronic meningitis before the definite diagnosis of PTCL, NOS

One case of EBV-associated LPD before the definite diagnosis of DLBCL

One case of Hashimoto thyroiditis found at the time of diagnosis of DLBCL of the thyroid gland

Three cases of IgG4-related disease found at the time of diagnosis of orbital marginal zone lymphoma

One case of chronic sclerosing sialadenitis (Kuttner tumor) at the time of diagnosis of plasmablastic lymphoma of the submandibular salivary gland and lymph node

One case of LPD with increased large B-cells in one SLE patient, not associated with EBV (EBER-) 5 years before the definite diagnosis of DLBCL

Two cases of lymphocytic thyroiditis before the definite diagnosis of thyroid lymphoma - one with extranodal MZL with plasmacytic differentiation and the other with DLBCL of the thyroid mass

Three cases of MGUS before the definite diagnosis of lymphoma - one with LPL and two cases with DLBCL

Two cases of monoclonal small B-cell lymphoid proliferation before the definite diagnosis of lymphoma - one with pulmonary MZL and the other with nodal SLL

Table 3 Interesting pathologic findings found during review (continued)**Failure to recognize lymphoma for a period of time before a definite diagnosis of lymphoma (13 cases)**

One case of ALK+ ALCL in a lymph node originally diagnosed as necrotizing granuloma, probably tuberculosis. This particular case has already been published as an interesting case report [Owattanapanich et al., 2017]

One case of mixed cellularity CHL in a lymph node originally diagnosed as granulomatous lymphadenitis

Four cases of DLBCL - one case failed to recognize small cell lymphoid neoplasm in the regional lymph nodes in the resection specimen of pulmonary adenocarcinoma 1 year ago, another case failed to recognize MZL in the thyroid specimen with the diagnosis of chronic thyroiditis 5 years ago, another case failed to recognize lymphoma in the marrow and misdiagnosed as myelodysplastic syndrome/myeloproliferative neoplasm (MDS/MPN) 1 year ago, and the other failed to recognize lymphoma in the lymph node infarction.

Two cases of FL - one case failed to recognize FL in the sentinel lymph node in a patient with CA breast 4 years ago and the other failed to recognize FL in a lymph node biopsy 1 year ago.

Three cases of extranodal MZL - 1 case in the lacrimal gland failed to recognize MZL (misdiagnosed as chronic inflammation) 4 years before the definite diagnosis, 1 case in the parotid mass that failed to recognize MZL (misdiagnosed as benign lymphoepithelial lesion) 5 years before the definite diagnosis, and 1 case failed to recognize MZL in the blind biopsy of ENT sites 4 years before the definite diagnosis from a cervical lymph node biopsy.

One case of nasal NK/T-cell lymphoma (NK/T) failed to recognize NK/T 3 years ago (misdiagnosed as ulcer with acute and chronic inflammation).

1 case of primary cutaneous ALCL failed to recognize the lymphoma and misdiagnosed as squamous cell carcinoma or chronic ulcer before the definite diagnosis.

Histologic transformation (44 cases)

DLBCL 37 cases - 32 cases with accompanying lymphomas listed previously (interpreted as large cell transformation), 3 cases with a history of lymphomas - one with primary cutaneous follicle center lymphoma 3 years ago, another with history of SLL/CLL for uncertain duration, and the other with history of indolent lymphoma diagnosed 19 years ago (no material for review) - and the other 2 cases with the 1 case failed to recognize small cell lymphoid neoplasm in the regional lymph nodes in the resection specimen of pulmonary adenocarcinoma 1 year ago, and the other case failed to recognize MZL in the thyroid specimen 7 years ago.

FL 4 cases - 1 case with Langerhans cell sarcoma 5 years later, 1 case with DLBCL in the brain 2 years later, 1 case with large cell transformation in the lymph node 3 years later and 1 case with 2 microscopic foci of large cell transformation in the duodenum (primary duodenal follicular lymphoma)

MALT lymphoma 2 cases - 1 case with large cell transformation (plasmablastic lymphoma morphology) 2 years later and 1 case with microscopic focus of large cell transformation

MF 1 case with large cell transformation

Second Malignancy (5 cases)

One case of nodular sclerosis CHL developed acute myeloid leukemia 8 years later at the age of 43 years.

One case of DLBCL found to have PTCL, NOS 5 years later at the age of 53 years

One case of treated lymphoma for 11 years (no available material for review) developed PTCL, NOS at the age of 64 years.

Table 3 Interesting pathologic findings found during review (continued)

One case of PTCL, NOS found to have metastatic large cell (non-small cell) carcinoma to supraclavicular lymph node at the same time of lymphoma diagnosis at the age of 36 years.

One case of SBCLN found to have metastatic adenocarcinoma in the same lymph node biopsy at the age of 75 years.

AITL: angioimmunoblastic T-cell lymphoma; ALCL: anaplastic T-cell lymphoma; BL: Burkitt lymphoma; CA: cancer/carcinoma; CHL: classical Hodgkin lymphoma; CLL: chronic lymphocytic lymphoma; DLBCL: diffuse large B-cell lymphoma; EBER: EBV-encoded small RNA; EBV: Epstein Barr virus; ENT: ear-nose-throat; FL: follicular lymphoma; HGBL: high-grade B-cell lymphoma; LPD: lymphoproliferative disorder; LPL: lymphoplasmacytic lymphoma; MALT lymphoma: extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue; MCL: mantle cell lymphoma; MF: mycosis fungoides; MGUS: monoclonal gammopathy of undetermined significance; MZL: marginal zone lymphoma; NK/T: extranodal NK/T-cell lymphoma; nLPHL: nodular lymphocyte-predominant Hodgkin lymphoma; PTCL, NOS: peripheral T-cell lymphoma, not otherwise specified; SBCLN: small B-cell lymphoid neoplasm; SLE: systemic lupus erythematosus; SLL: small lymphocytic lymphoma

mation, or ulcers have been well documented as risks or predisposing factors in lymphomagenesis. Moreover, altered immune status, especially immunodeficiency states, drug reactions, chemical exposure and others also play role in lymphomagenesis as well.²⁻¹² At times, the clinical information of immunodeficiency states or iatrogenic immunodeficiency makes diagnosing lymphoma more difficult because the pathologic features are commonly perplexing and the most important differential diagnosis is posttransplant LPDs. When complete studies cannot be performed, a careful approach should prevent overdiagnosis of lymphoma. Adjusting immunosuppressive drugs to improve immune status may clear up the lymphoproliferative lesion.¹ In addition, among some patients, previous clinical history was not related to lymphoma such as benign tumor, hyperplasia and cystic lesion.

Interestingly, 32 of 411 cases of DLBCL (7.8%) were found to have accompanying lymphoma of other types, mostly indolent B-cell lymphomas, including FL (53.1%), MZL (28.1%), SLL (9.4%), SBCLN (3.1%), and LPL (3.1%). One case of DLBCL with accompanying AITL was also found in this study. This phenomenon has been known as histologic transformation in lymphoma, especially when 2 lymphoma types with different grades are found

in the same pathology samples or separately during a short period of time, for example, large cell lymphoma in a lymph node biopsy but small cell lymphoid neoplasm in the marrow at the time of staging, commonly known as cytologic discrepancy between primary lesion and marrow.^{16,17} Moreover, in this study, large cell transformation was found in two cases of MALT lymphoma and one case of MF. This observation emphasizes the careful search for accompanying lymphoma or histologic transformation that may be overlooked when not obvious.

Among the 999 lymphoma patients, 20 cases (2.0%) were found to have different subtypes upon review as shown in Table 3. This number was less than those reported in the literature^{18,19} because most of the final diagnoses of lymphoma cases given by pathologists at Siriraj Hospital have been supported by morphology and appropriate panel of immunohistochemistry (immunostaining) with satisfactory technical quality.^{20,21} Nevertheless, less experienced pathologists might be challenged recognizing some features in particular lymphoma types (for example, clear cells in AITL vs. monocytoïd cells in MZL), proper interpretation of the immunostaining results (for example, CD5 expression in SLL), or inappropriate panel of immunostaining (too

few or too many markers). One highly concerned issue from the incorrect subtyping of lymphoma is failure to recognize high grade features in lymphoma by morphology. A small area of starry sky pattern or nuclear debris in the background should be searched for - the former by low magnification (4x objective) and the latter by high magnification (40x or 60x objective). Another morphologic recognition is nuclear details of blastic/blastoid features with delicate nuclear membrane and dispersed, fine nuclear chromatin with or without nucleolus. Immunostaining for Ki-67 and TdT may be helpful to determine the proliferation index and immature (precursor) phenotype of lymphoma cells, respectively.^{22,23}

Preceding lymphoproliferative disorders (LPDs) were detected in 20 cases (2.0%) before definitely diagnosing lymphoma in subsequent pathology samples. Some are so important that proper investigation, at least immunostaining, may help to confirm LPDs and appropriate work-up or follow-up can be provided to supplement patient care. In this study, three cases of primary cutaneous CD30+ LPDs were found; one patient was eventually diagnosed as primary cutaneous ALCL six years later. Two cases of monoclonal small B-cell lymphoid proliferation were identified before the definite diagnosis of lymphoma - one with pulmonary MZL and the other with nodal SLL - examples of tissue-based monoclonal B-cell lymphocytosis, a newly proposed entity in the WHO classification (revised 4th edition, 2017).¹ In one particular patient with SLE, a diagnosis of nonEBV LPD with increased large B-cells was given according to the awareness of immunosuppression condition at the time of biopsy. Later, this patient experienced off-and-on lymphadenopathy and eventually, five years later, a definite diagnosis of DLBCL was established and the disease was defined as refractory. Distinguishing between LPD and DLBCL more precisely is possible in this particular situation. Flow cytometry or molecular genetic studies can help to detect an abnormal lymphoid clone but how strong the results are indicative of lymphoma are arguable.

Certainly, these results are not accepted as a true diagnosis of lymphoma when the patient has spontaneous recovery after excision of the enlarged lymph node. At present, clinical correlation is still the most important indicator to guarantee the malignant behavior of lymphoma.

In all, in this study, pathologists failed to recognize lymphoma 13 cases for a period of time before a definite diagnosis of lymphoma was given. The first scenario involved two cases masking by granulomatous reaction. One case of ALK+ ALCL in a lymph node was originally diagnosed as necrotizing granuloma, probably tuberculosis. This particular case had already been published as an interesting case report.²⁴ The other case involved mixed cellularity CHL in a lymph node originally diagnosed as granulomatous lymphadenitis. To avoid the failure to recognize lymphoma in granulomatous reaction background, pathologists should be aware of lymphoma when mitosis is found within the granuloma because the proliferation index is low involving granulomatous reaction in tuberculous lymphadenitis.²⁵ Another scenario involved failure to recognize indolent lymphoma in the lymph node dissection specimen for other nonhematologic malignancy²⁶⁻²⁸ in two cases, one with small cell lymphoid neoplasm in a patient with pulmonary adenocarcinoma one year ago (having large cell transformation as DLBCL at the time of lymphoma diagnosis) and the other with FL in the sentinel lymph node in one patient with CA breast four years ago (still FL at the time of lymphoma diagnosis). One may wonder how pathologists miss indolent lymphoma in the lymph node dissection along with resection of carcinoma. The explanation should be a phenomenon called "inattention blindness" that might explain why indolent lymphoma was not recognized during the search for metastatic carcinoma, usually by screening at low magnification of the lymph node dissection.²⁹ To prevent this failure to recognize indolent lymphoma, pathologists should pay attention to the changes of the lymphoid cell component in the lymph node after finishing the search for metastatic carcinoma.

Another common scenario occurs when lymphoid infiltrative or proliferative lesion cannot be diagnosed as lymphoma by various reasons. In this study, 8 cases included MZL (four cases of thyroid gland, lacrimal gland, salivary gland, or blind biopsy of ENT sites), DLBCL (one case in an infarcted lymph node), FL (one case in a lymph node biopsy), NK/T (one case in a chronic ulcer), and primary cutaneous ALCL (one case in a chronic ulcer). The case with MZL not recognized in thyroid gland had focal involvement of the lymph nodes in the thyroid specimen from a patient with an original diagnosis of chronic lymphocytic thyroiditis five years ago. Later, large cell transformation as DLBCL was given at the time of lymphoma diagnosis. Lymph node infarction is one diagnostic problem in pathology practice and lymphoma is one of the most common causes that needs to be searched for.³⁰

The last scenario involved an unexpected case from clinical aspects. Only one case in this study involved DLBCL in the bone marrow but the large lymphoma cells were misinterpreted as immature myeloid precursors by morphology as the patient was clinically expected to have MDS/MPN. Increased risk of lymphoproliferative disorder has been found in MPN³¹ and recently was proposed in WHO classification (revised 4th edition, 2017) as myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRA*, *PDGFRB*, or *FGFR1*, or with *PCM1-JAK2*.¹

In this study, 44 cases involved histologic transformation, 43 had large cell transformation (42 cases in B-cell lymphoma and 1 case in T-cell lymphoma) and only one with Langerhans cell sarcoma. Pathologists should be aware of histologic transformation in malignant lymphoma even though the relationship between the indolent lymphoma and the aggressive lymphoma commonly described in the literature may not be proven to originate from the same clone.^{16,17}

Second malignancy is the last pathologic finding that pathologists should search for, especially among patients with lymphoma treated for years or among

elderly patients with increased risk of having a second malignancy.

Summary

In conclusion, this retrospective study demonstrated pathologic findings known before diagnosing malignant lymphoma that raise concerns regarding developing routine practice guidelines to prevent misdiagnosis as discussed above.

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