

Incidental Malignant Lymphoma and Lymphoproliferative Disorders in Lymph Node Dissection Specimens during Tumor Removal in Various Organs

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ABSTRACT

Objective: To find incidental malignant lymphoma and lymphoproliferative disorders (LPD) in lymph node dissection specimens during tumor removal in various organs.

Methods: A review was performed separately by two pathologists in two rounds of all H&E-stained slides of lymph nodes found during the removal of solid tumors at Siriraj Hospital: the first round concentrating on the detection of any metastatic tumor cells in lymph node sinuses and the second round concentrating on any incidental lymphoma or LPD. Then, the results were compared to reach consensus. Immunohistochemical studies were performed to help confirm the diagnosis of lymphoma or LPD.

Results: In total, 309 cases were reviewed. Lymph nodes were taken out during surgical tumor removal of the breast (110 cases), colon and rectum (57 cases), female genital organs (41 cases), lung (20 cases), thyroid (20 cases), oral cavity (16 cases), prostate (14 cases), and others (31 cases). Only 1 case (0.3%) was found to have follicular lymphoma, while 4 cases (1.3%) were found to have LPD, including in situ follicular neoplasia (1 case), suspected follicular lymphoma (1 case), and marginal zone hyperplasia (2 cases). An experienced pathologist was able to detect incidental lymphoma and LPD.

Conclusion: Incidental lymphoma and LPD can be found in lymph node dissection specimens. Attention should thus be paid during histologic evaluation to find any incidental lymphoma or LPD for another round of lymph node screening after finishing the search for metastasis in the lymph node dissection or sentinel lymph node biopsy to avoid “inattentive blindness.”

Keywords: Incidental lymphoma; lymphoproliferative disorders; lymph node dissection; solid tumor; inattentive blindness (Siriraj Med J 2020; 72: 103-108)

INTRODUCTION

Based on research conducted on malignant lymphoma at Siriraj Hospital in the past decades, one of the authors (SS) has been publishing pathologic data regarding

malignant lymphoma in Thai people in international medical journals since 1998.¹ Moreover, the same author published a report in an international medical journal in 2004 on malignant lymphoma types in Thai people

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diagnosed from this single institution in up to 1,983 cases.² Further studies have been periodically published regarding various aspects of malignant lymphoma in Thai people.³⁻¹⁰ Interestingly, the information from Siriraj Hospital on malignant lymphoma in Thai people is comparable to the data reported from a later collaborative study of malignant lymphoma in Thai people among many medical centers in Thailand,¹¹ which is perhaps not surprising as Siriraj Hospital is the largest government-based hospital (2,000 in-patient beds) in Thailand and is equipped with its own pathology laboratory, rendering the institute higher chances of obtaining pathology specimens and encountering a wider range of malignant lymphoma than in smaller hospitals. Furthermore, the existence of a great number of patients with long follow-up visits allows an appreciation of disease variations along the clinical course or any related conditions or emerging morbidities. Also it is possible to note incipient lesions encountered in previous pathology specimens taken from the patients before they developed overt lymphoma. Recently, the same author (SS) has published the results of the study on “Pathologic findings prior to the diagnosis of malignant lymphoma – a retrospective study in a large medical institute” based on a review of all previous pathology slides prior to the definite diagnosis of malignant lymphoma, with an aim to search for any lymphoma or lymphoproliferative disorder that might have been missed in the initial diagnosis. Among the 999 lymphoma patients who made at least one visit to Siriraj Hospital for a definite diagnosis or follow-up, there were two lymphoma patients who had a previous history of cancer, one with a lobectomy for lung cancer and the other with mastectomy for breast cancer. Upon reviewing the lymph node dissection slides on these two patients, it was found that both had already had lymphoma in those lymph nodes but they were missed by the original pathologists: one a case of diffuse large B-cell lymphoma (DLBCL), where the pathologist had failed to recognize a small cell lymphoid neoplasm in the regional lymph nodes in the resection specimen of pulmonary adenocarcinoma 1 year earlier, and another case of follicular lymphoma (FL) in the sentinel lymph node in a patient with CA breast 4 years earlier.¹² These missed diagnoses can be explained by the perceptual phenomenon described as “inattentional blindness”,¹³ whereby the attention of the pathologist at the time was only on the metastatic tumor cells, mostly confined in lymph node sinuses, while the other portions of the lymph node were neglected (overlooked or “blind”). So the lymphoma was not reported at that time.¹²

After the aforementioned study, 4 more cases were found during hematopathology services at Siriraj Hospital by one of the authors (SS), namely: 1) a newly diagnosed case of chronic lymphocytic leukemia (CLL) found to have already had small lymphocytic lymphoma (SLL) in the lymph node dissection specimen taken for prostatic adenocarcinoma performed 6 years previously, but missed by the attending pathologist at that time; 2) a case of CLL proven to have nasopharyngeal involvement by tissue biopsy, which also had the involvement of all the lymph nodes in the lymph node dissection specimen taken for pulmonary adenocarcinoma in the following few months, but was missed by the attending pathologist at the time (the surgeon failed to inform the underlying CLL to the pathologist); 3) a case of mantle cell lymphoma (MCL) with the involvement of all the lymph nodes of a lymph node dissection specimen taken for pulmonary adenocarcinoma several months later, but was initially missed by the attending pathologist; and 4) a known case of rectosigmoid adenocarcinoma that had follow-up colonoscopy 2 years later and was found to have multiple polyps. The polypectomy specimen was shown to have extranodal marginal zone lymphoma of the mucosa-associated lymphoid tissue (MALT lymphoma). Then, a review of the previous surgical removal of the rectosigmoid adenocarcinoma revealed that the lymph nodes involved marginal zone lymphoma but no MALT lymphoma was detected in any colonic mucosa taken for histologic evaluation. No polyp was found in the resection specimen at that time.

These incidental lymphoma cases prompted the authors of the present study to review the literature, which revealed that the frequency of incidental lymphoma in lymph node dissection ranged from 0.2% to 1.6% of cancer patients who underwent tumor removal.¹⁴⁻²⁰ Most previous studies were conducted in prostatic cancer patients (0.2–0.4%),¹⁴⁻¹⁷ and only three studies were conducted in melanoma patients (0.3%),¹⁸ head & neck cancer patients of the squamous cell carcinoma type (1.5%),¹⁹ and breast cancer patients (1.6%).²⁰ Given this possible incidence reported in the literature, it would be interesting to know whether lymph node dissection in cancer patients performed at Siriraj Hospital could result in any chance of missed incidental lymphoma or lymphoproliferative disorders (LPD).

MATERIALS AND METHODS

The pathologic diagnosis of lymphoma given in this study followed the WHO classification based on clinical, morphologic, immunophenotypic, and genetic findings.²¹

Nevertheless, due to some limitations, especially in genetic studies, the diagnoses in this study were given primarily based on the morphologic and immunophenotypic findings. Table 1 shows the list of antibodies for the lymphoid markers used for immunohistochemistry in the present study.

After receiving a certificate of approval for this study from the Siriraj Institutional Review Board (Si 289/2018), a search of the laboratory information system used at Siriraj Hospital, known as “HCLAB”, was conducted by one of the authors (SS) only. All the slides available in the archive room were retrieved. After that, both authors (SS and WMO) independently performed histologic reviews of the slides without any communication between them. They performed their reviews in two rounds: the first round concentrated on the detection of any metastatic tumor cells in lymph node sinuses, while the second round concentrated on the lymph node changes to detect any incidental lymphoma or LPD. After both authors had finished their pathology reviews independently, a comparison of the results was performed to reach consensus.

RESULTS

The project had to be completed within a one-year training period to fit in with a hematopathology fellowship program followed by one of the authors (WMO) under the tutelage of the other author (SS). Due to the time constraint, only 309 cases in total could be reviewed. The

demographic data are summarized as follows: female to male ratio, 2.5 (221 to 88); ages of the patients, 21 to 91 years old (median, 60 years old; mean, 59.7 years old); organs with tumor removal: the breast (110 cases), colon and rectum (57 cases), female genital organs (41 cases, including the uterus in 25 cases, ovary in 11 cases, and uterine cervix in 5 cases), lung (20 cases), thyroid (20 cases), oral cavity (16 cases), prostate (14 cases), larynx (8 cases), skin (5 cases), stomach (5 cases), liver (4 cases), pancreas (3 cases), kidney (3 cases), tonsil (1 case), small intestine (1 case), and eyeball (1 case).

There were 5 cases found of incidental lymphoma and lymphoproliferative disorders in lymph node dissection specimens during tumor removal. The results are presented in Table 2. There was 1 case of follicular lymphoma (FL) at the time of first diagnosis of endometrial carcinoma by the original pathologist. Here, the reviews by the two authors concurred with the diagnosis of crowded neoplastic lymphoid follicles with the BCL2+, CD10+, and CD20+ phenotypes typically seen in FL. This patient was a 55-year-old female, who was lost to follow-up following discharge after surgical tumor removal, so the hematologic work-up for a complete clinical staging was lacking. Then there were 4 cases recognized to be abnormal by the experienced hematopathologist (SS) only: 2 suspicious of FL and 2 suspicious of small cell lymphoid neoplasm (SCLN) with a mantle/marginal zone configuration. Immunostaining showed that 1 of the 2 suspected cases of FL turned out to be *in situ*

TABLE 1. List of antibodies for lymphoid markers used for immunohistochemistry in the present study.

Antibody to	Marker for	Remarks
CD3	T-cells	Common T-cell marker
CD5	T-cells	Aberrant expression in B-cell neoplasms
CD10	B-cells & T-cells	Germinal center B-cell & T follicular helper
CD20	B-cells	Common B-cell marker
CD23	B-cells & FDC	FDC meshwork in reactive germinal center
Cyclin D1	Cell cycle protein	Expressed in neoplastic mantle cells
BCL2	Anti-apoptotic protein	Expressed in neoplastic germinal center cells and various types of lymphomas
Kappa light chain	Ig, light chain	Expressed in some plasma cells
Lambda light chain	Ig, light chain	Expressed in some plasma cells
IgD	Ig, delta heavy chain	Expressed by naive B-cells in mantle layer

Abbreviations: FDC: follicular dendritic cells; Ig: Immunoglobulin

TABLE 2. Incidental lymphoma and lymphoproliferative disorders in lymph node dissection specimens during tumor removal (total of 5 cases).

Case (age/sex)	Tumor removal	Incidental lymphoma/LPD	Recognized by
#1 (55/F)	Endometrial carcinoma	Follicular lymphoma, low grade	Original pathologist, SS, WMO
#2 (74/F)	invasive ductal carcinoma of breast	In situ follicular neoplasia	SS only
#3 (68/M)	CA rectum	Suspected follicular lymphoma	SS only
#4 (67/F)	Endometrial carcinoma	Marginal zone hyperplasia	SS only
#5 (80/F)	Endometrial carcinoma	Marginal zone hyperplasia	SS only

Note: There was no metastatic carcinoma in any of the lymph nodes in these 5 cases.

Abbreviations: SS: Sanya Sukpanichnant; WMO: Win Myat Oo

follicular neoplasia (but this was still queried as low grade FL) as shown by the few BCL2+, CD10+, and CD20+ neoplastic lymphoid follicles located close to one another, but not typically as crowded as those found in FL. This patient was a 74-year-old female who had invasive ductal carcinoma of the breast. The other suspected case of FL failed to show any BCL2 protein expression, even when using 2 clones of antibodies for BCL2 (clone 124 and clone E17) in the crowded lymphoid follicles. The 2 suspected cases of SCLN with a mantle/marginal zone configuration were pelvic lymph nodes that had hyalinized vessels. They turned out to be marginal zone hyperplasia (MZH) after immunostaining with the help of IgD to separate the lymphoid cells in the mantle layer from the lymphoid cells in the MZH. Both patients, aged 67 and 80 years old, respectively, were diagnosed as endometrial carcinoma. All of these 4 abnormal cases did not have any further submission of a pathological sample after surgical tumor removal up to the time of the manuscript preparation on August 23, 2019. In all these 5 cases in Table 2, there was no evidence detected of metastatic carcinoma in the lymph node.

In summary, only 1 out of 309 cases was proven to have low grade FL (0.3%). The other 2 cases of suspected FL were proven to be *in situ* follicular neoplasia (1 case) and a still questionable case of FL (1 case). The other 2 cases of suspected SCLN were proven to be MZH. If these 4 cases are considered as LPD, then the incidence of incidental LPD was 1.3%.

DISCUSSION

Incidental lymphoma and LPD can be found in lymph node dissection specimens during tumor removal

in various organs, as shown in the results above. From the present study, incidental lymphoma was found in 0.3% of the 309 cases evaluated, which is an incidence not different from those reported in the literature.¹⁴⁻²⁰ However, its early recognition is important, leading either to hematologic work-up for a complete clinical staging when the incidental lymphoma is established or to searching for a definite lymphoma diagnosis when incidental LPD is found. Most of the incidental lymphoma cases reported in the literature and in this study have been indolent lymphomas without any systemic symptoms, such as SLL/CLL, follicular lymphoma, or marginal zone lymphoma.¹⁴⁻²⁰ Since the conventional management in asymptomatic indolent lymphoma is usually to adopt a “watch and wait” policy,²² it seems that incidental lymphoma found in lymph node dissection specimens during tumor removal in various organs may not be an issue of concern in terms of clinical significance. But, in fact, it does matter, as large cell transformations can occur in a number of indolent lymphoma patients.²³ In our experience and as already published, one case of DLBCL involved a failure to recognize small cell lymphoid neoplasm (SCLN) in the regional lymph nodes in the resection specimen of a patient with pulmonary adenocarcinoma 1 year earlier.¹² It would have been much better if the indolent lymphoma (SCLN) was recognized at the time of CA lung resection and the patient had undergone hematologic work-up for a complete clinical staging and proper management, including follow-up. The problem found in these patients after surgical tumor removal is a loss of adequate follow-up as the patients may believe that they are cured; for instance, all 5 patients in the study shown in Table 2 did not have any further

submission of a pathological sample after surgical tumor removal.

According to the WHO classification (revised 4th edition, 2017),²¹ “*in situ* follicular neoplasia (ISFN)” is defined as partial or total colonization of germinal centers by clonal B-cells carrying the *BCL2* translocation characteristic of follicular lymphoma (FL) in an otherwise reactive lymph node. For patients with incidentally diagnosed ISFN and no other evidence of FL upon clinical evaluation, the risk of subsequent FL is very low ($\leq 5\%$). By morphology alone, it is difficult to recognize ISFN, and the affected follicles composed almost exclusively of centrocytes (closely packed centrocytes) may be the only histologic clue for ISFN. Certainly, immunohistochemistry for *BCL2* and *CD10* will show *BCL2*+ centrocytes exclusively in the affected follicles, with a higher intensity than in adjacent T-cells or cells in the mantle layer. These *BCL2*+ centrocytes will also show an increased expression of *CD10*. Thus, according to the aforementioned findings, ISFN could be diagnosed without the need for genetic studies to confirm the diagnosis. But, if any genetic profiles are needed, ISFN cells are positive for t(14;18) or mutations in *EZH2*.

For the other case of “suspected follicular lymphoma (FL),” the morphology was quite typical for FL, but in this particular case, the lymphoma cells lacked the expression of the *BCL2* protein, even when using the 2 clones of antibodies for *BCL2* (clone 124 and clone E17). This phenomenon is at times seen in daily practice and it can happen when secondary events lead to mutations in *BCL2*, resulting in a negative staining of FL with the commonly used clone 124 antibody to *BCL2*. According to the WHO classification,²¹ the absence of *BCL2* protein does not exclude the diagnosis of FL. Other germinal center markers, including *LMO2*, *GCET1*, and *HGAL*, will be positive in these cases. Determination of surface immunoglobulin (sIg) by flow cytometry can be helpful to establish evidence of neoplastic follicular center cells. However, in this study, this particular case of “suspected FL” did not have confirmation done by using any other germinal center markers or the determination of sIg by flow cytometry because the morphology and the *CD10*+ and *BCL6*+ phenotypes in the lymphoma cells seemed to be sufficient to designate this case as “suspected FL.”

Regarding the 2 cases of marginal zone hyperplasia (MZH) in the study, the literature emphasizes excluding MZH before making a diagnosis of nodal marginal zone lymphoma (NMZL). The identification of three separate zones, namely the innermost pale zone of the reactive germinal center, the dark staining mid zone of the mantle layer, and the outermost pale zone of the marginal zone,

without distortion of other lymph node compartments or pericapsular infiltration should lead to a concern of MZH. The B-cells in MZH are frequently negative for *BCL2* and *CD43*. Plasma cells should be polyclonal in MZH. In case of doubt, flow cytometry or a molecular study for the clonal rearrangement of the immunoglobulin heavy chain gene would be helpful to distinguish MZH from NMZL. MZH should lack monoclonal evidence.^{24,25} Since MZH of the lymph node is rare, it is quite difficult to find the causes. However, the following causes have been described in the literature: *Haemophilus influenzae* infection (6 cases),²⁶ EBV infection (1 case),²⁷ and systemic bacterial infection (1 case).²⁸ In addition, associated conditions found at the time of lymph node swelling were chronic tonsillitis (1 case) and hepatocellular carcinoma (1 case).²⁴

The present study does support the “inattentional blindness” phenomenon¹³ as attention was only on the metastatic tumor cells, mostly confined in lymph node sinuses, while the other portions of the lymph node were neglected (overlooked or “blind”) as proposed by one of the authors (SS).¹² Also it was observed in the study that recognition of the histologic findings of various types of lymphoma and LPD plays an important role in enabling pathologists to suspect incidental lymphoma or LPD in lymph node dissection specimens during tumor removal in various organs. In order to overcome the “inattentional blindness” phenomenon during histologic evaluation of lymph node dissection specimens during tumor removal in various organs, it is recommended that pathologists look at all histologic sections of the lymph nodes in a second round for any incidental lymphoma or LPD after searching for metastatic tumor in the first round. Certainly, improving the recognition of the histologic findings of various types of lymphoma and LPD by an individual pathologist may be difficult to achieve as it is personal capability, but continuing education may enhance this capability.

CONCLUSION

Despite the low incidence of incidental lymphoma, it is more beneficial for patients if pathologists can detect lymphoma in the lymph node dissection during the surgical removal of solid tumors. The findings from the present study raise some suggestions on ways to enhance the detection of incidental lymphoma, including: 1) paying specific attention to be able to find any incidental lymphoma in a second round of lymph node screening after finishing the search for metastasis in the lymph node dissection or sentinel lymph node biopsy in a first round, in order to avoid “inattentional blindness;¹³ and

2) having a greater awareness of the morphology features in lymphoma and LPD. The latter requires more interest in hematopathology among general pathologists, as experienced hematopathologists may already be aware of more varieties in lymphoma and LPD during screening.

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