The importance of second opinion in surgical pathology referral material of lymphoma

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ABSTRACT

الأهداف: لتقييم أهمية الرأي الثاني لعلم الأمراض في تشخيص سرطان الغدد الليمفاوية واستعراض الأمراض التي تحاكي هذا الورم.

الطريقة: لقد تمت مراجعة حالات تشخيص علم الأمراض للمرضى المحولين لعلاج سرطان الغدد الليمفاوية إلى اثنين من مستشفيات الرعاية من الدرجة الثالثة في المنطقة الغربية من المملكة العربية السعودية وهي مستشفى جامعة الملك عبدالعزيز، ومستشفى الملك فيصل التخصصي، جدة خلال 10 سنوات (أغسطس 2001 إلى أغسطس 2011). وقد شملت هذه الدراسة الحالات التي حولت للعلاج فقط.

النتائج: أشارت نتائج الدراسة إلى أن من أصل 560 حالة حولت لعلاج سرطان الغدد الليمفاوية فقد كان التشخيص بالرأي الثاني مختلفاً بدرجة واضحة عن التشخيص الأولي من المستشفى المحول في 39 حالة (7%). ويشمل هذا تغيير تشخيص الأورام اللمفاوية من سرطان الغدد الليمفاوية إلى تغيرات حميدة، وتغيير نوع الليمفوما ذات التأثير الكبير على الناحية السريرية العلاجية، وتغير التشخيص من عدم القدرة على التشخيص أو تغيرات حميدة إلى سرطان الغدد الليمفاوية.

خاتمة: أثبتت الدراسة بأنه يمكن للرأي الثاني لورم الغدد اللمفاوية أن ينتج تعديلات رئيسية في العلاج مع تأثيرات كبيرة على الناحية البشرية والمالية. وبالتالي فمن المستحسن مراجعة العينات النسجية قبل قرار العلاج لتحقيق أقصى قدر من اكتشاف الخلافات الرئيسية ذات الأهمية السريرية. يعد التقيد الصارم لسياسة المؤسسة بإلزامية الرأي الثاني لعلم الأمراض مهم لضمان الجودة في علم الأمراض النسيجي.

Objectives: To evaluate the importance of inter-institutional second opinion surgical pathology review of lymphoma, and identify the lymphoma pathologic mimics.

Methods: The surgical pathology material of patients referred to 2 tertiary care hospitals in the western region of Saudi Arabia (King Faisal Specialist Hospital and Research Centre and King Abdulaziz University Hospital, Jeddah, Saudi Arabia), for evaluation or therapy for lymphoma over a 10-year period (August 2001 to August 2011), were reviewed. This study included only cases in which the patient referred with a diagnosis previously made at the primary institution.

Results: Of 560 cases, the second opinion diagnosis differed significantly from the initial diagnosis in 39 cases (7%). These include changing the diagnoses from lymphoma to non-lymphoma lesions, change the type of lymphoma with major clinical impact, and change from reactive/non-diagnostic to lymphoma.

Conclusion: Second opinion surgical pathology for lymphomas can result in major therapeutic and prognostic modifications. Thus, review of the original histologic material is recommended prior to a major therapeutic decision, and to maximize the discovery of clinically relevant major disagreements. Stringent adherence to institution's second opinion policy is an important quality assurance measure in surgical pathology.

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Correct histopathologic diagnosis is essential for adequate treatment of lymphomas. In today's practice of medicine, it is common for patients to have pathology diagnosis at one hospital and subsequent therapy at another, which usually are tertiary centers. When this happens, experienced pathologists at the managing institution usually review the pathology materials. The principal motivation for second opinion is to improve patient care. Although many institutions have a policy of internal review of the pathologic material prior to treatment, this policy may be disregarded by some treating clinicians, not enforced by the institutions administration.[1] This issue has not been addressed in literature in the Kingdom. The aim of this study is to evaluate the importance of inter-institutional second opinion surgical pathology review of lymphoma and identify the lymphoma pathologic mimics in the referral pathology material that was sent to 2 tertiary care hospitals in the western region of Saudi Arabia.

Methods. The surgical pathology material of patients referred to 2 tertiary care hospitals in the western region of Saudi Arabia (King Faisal Specialist Hospital and King Abdulaziz University Hospital, Jeddah, Saudi Arabia) for evaluation or therapy for lymphoma over a 10-year period (August 2001 to August 2011), were reviewed. Ethical approval was obtained from the research ethics committee.

This study included only cases in which the patient had a diagnosis previously made at the primary institution. Cases sent in for second opinion as true consults in which the outside pathologist was unsure of the diagnosis or cases sent for ancillary tests were excluded from this study. The outside histopathologic slides were sent in from different laboratories including private and governmental hospitals and independent laboratories.

Significant differences or major discrepancies were defined as those that had a significant impact on therapy or had a prognostic implication, which included changes from malignant lymphoma to benign process or vice versa or changing the type of lymphoma to a different one with major clinical significance.

Statistical analysis. Data were analyzed using the Statistical Package for Social Sciences (SPSS Inc, Chicago, IL, USA) version 16.

To evaluate the agreement between the original and review diagnoses; interpretation of the agreement by Kappa value was carried out by using the following intervals: <0.4 poor-to-fair agreement, 0.4-0.6 moderate agreement, 0.6-0.8 substantial agreement, and $p>0.8$ almost perfect agreement. (please rephrase)

Results. Of 560 cases, the second opinion diagnosis differed significantly from the initial diagnoses in 39 patients (7%). In those cases, the diagnosis was changed from lymphoma to non-lymphoma diagnosis, which included benign or non-lymphoid malignancy (23 patients), or type of lymphoma was changed to another type that carry a clinical significance (11 patients). On the other hand, in 5 patients the diagnosis was changed from reactive/inflammatory or non-diagnostic to lymphoma on the second review diagnosis. Summary of the review diagnosis is presented in **Table 1**. Overall, there was a moderate agreement (Kappa value= 0.564) between the original diagnosis and second opinion review diagnosis.

The second opinion diagnoses review that were benign or reactive included Kikuchi-Fujimoto's disease (KFD), Castleman's disease (CD), progressive transformation of germinal centers (PTGC), reactive lymphoid follicular hyperplasia, atypical interfollicular lymphoid proliferation, infectious mononucleosis (IMN), and Hashimoto's thyroiditis. The non-lymphoid malignancies included granulocytic sarcoma, (GS), dendritic cell tumor (DCT), thymoma, carcinoma, high-grade uterine sarcoma and melanoma (**Figures 1a-1f**). In 11 patients, the review diagnosis was a different type of lymphoma than the original diagnosis, which has a clinical implication. This included changing Hodgkin's lymphoma to Non-Hodgkin's lymphoma (2 patients), Non-Hodgkin's lymphoma to Hodgkin's lymphoma (3 patients), diffuse large B-cell lymphoma to high-grade Burkitt's-like lymphoma (3 patients), low-grade follicular lymphoma to high-grade follicular lymphoma (1 patient) and T-cell lymphoma to B-cell lymphoma (2 patients). Disagreement on the type of lymphoma with no major impact on therapy was seen in an additional 14 patients and examples of those cases include changing the subtype of Hodgkin's lymphoma or Grade I versus Grade II follicular lymphoma.

Discussion. In this study, the review diagnosis was straightforward morphologically or supported by certain ancillary tests such as immunohistochemistry or molecular studies. In 3 patients, the review diagnosis was confirmed by an expert opinion (consultation from Mayo clinic, United States), while in another 3 patients, the review diagnoses were supported by re-excision of lesion. In those cases with re-excision, the diagnoses

Table 1 - Second opinion review diagnoses of patients with change of diagnoses from lymphoma to non-lymphoma lesions.

Review diagnosis	Number of cases	Location
Kikuchi-Fujimoto's disease	4	Lymph nodes
Castleman's disease	2	Lymph nodes
Progressive transformation of germinal centers	2	Lymph nodes
Granulocytic sarcoma	2	Duodenum, breast
Dendritic cell tumor	1	Stomach
Reactive lymphoid follicular hyperplasia	2	Lymph node
Atypical interfollicular lymphoid hyperplasia	3	Lymph node (2), tonsils (1)
Infectious mononucleosis	1	Spleen
Hashimoto's thyroiditis	1	Thyroid
Poorly differentiated carcinoma	1	Stomach
Anaplastic thyroid carcinoma	1	Thyroid
High-grade uterine sarcoma	1	Uterus
Melanoma	1	Rectum
Thymoma	1	Mediastinum
Total	**23**	

were suggested in the second opinion review; however, re-excision was confirmatory. The most common mimic of lymphoma in this study was KFD, where 4 cases have been initially misdiagnosed as lymphoma (3 T-cell lymphoma and 1 Hodgkin's lymphoma). Recognition of this entity is crucial, because mistaking this disease as lymphoma has major clinical consequences. The main misleading feature in KFD that resulted in misdiagnosis in these cases was the presence of proliferating immunoblasts. The pathological diagnostic challenges of KFD have been clearly addressed in the literature.[2] Three of KFD patients in this study have been initially labeled as T-cell lymphoma which is the most common suspected diagnosis in KFD.[3] Specimens from 4 patients showed incomplete architectural effacement with patchy involvement that revealed abundance of karyorrhectic debris, presence of immunoblasts and histiocytes with crescent shaped nuclei. Immunohistochemistry was helpful to support the diagnosis of KFD in these patients. In 4 cases, there was a predominance of CD8-

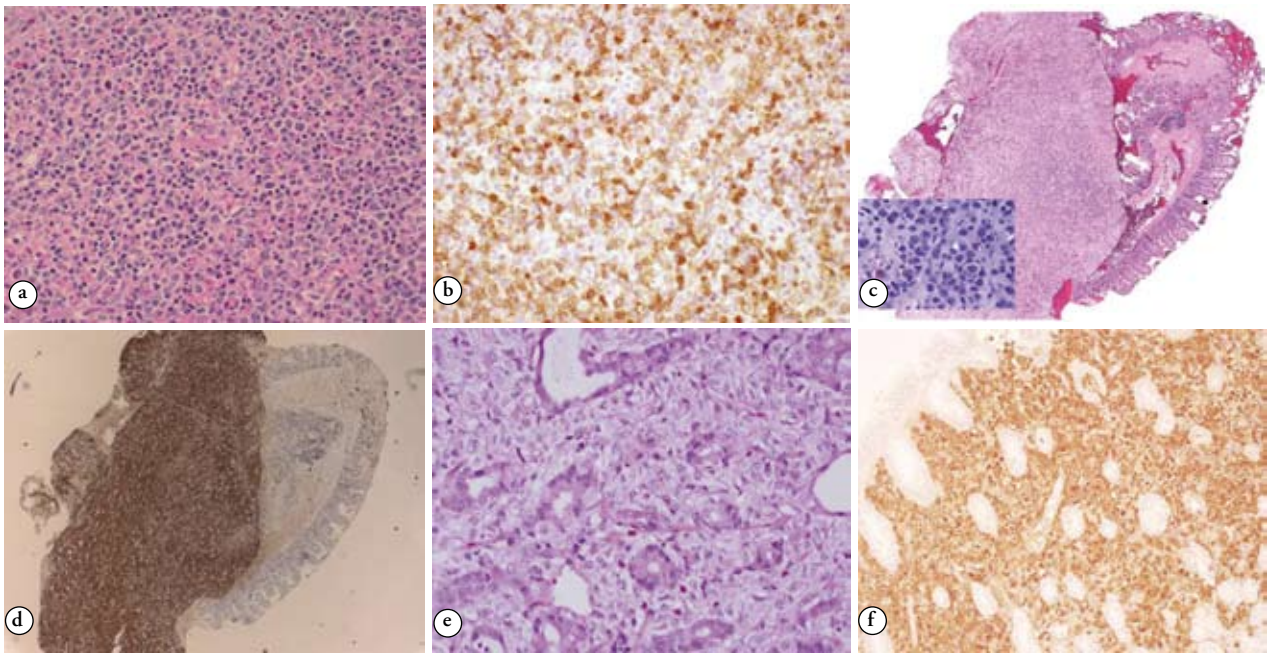

Figure 1 - **a**) Lymph node involved by a proliferative pattern of Kikuchi-Fujimoto's disease (KFD) with numerous transformed lymphocytes (immunoblasts) and with some characteristic karyorrhectic debris (hematoxylin-eosin, original magnification x400). **b**) Immunohistochemistry stain for CD3 for the same case of Figure 1a reveals many positive large T-cells, which give the initial impression of T-cell lymphoma; however, the other characteristic morphological and immunohistochemical features confirm the diagnosis of KFD (original magnification x400). **c**) Duodenal biopsy reveals dense neoplastic infiltrate in the wall, inset reveals individual large hematolymphoid cells. This case was interpreted initially as a large cell lymphoma. **d**) Immunohistochemistry stain for myeloperoxidase for the same case of figure 1c, reveals positive staining for myeloperoxidase in the tumor which together with other markers are consistent with granulocytic sarcoma (original magnification x100). **e**) Gastric biopsy reveals a tumor that infiltrates between the gastric glands. The tumor cells have round to oval vesicular nuclei. The tumor cells are weakly positive for CD45 and negative for Pankeratin and CD117. The tumor initially misdiagnosed as large cell lymphoma (original magnification x400). **f**) Immunohistochemistry stain for S100 for the same case of figure 1e reveals positive staining. This case was diagnosed as interdigitating dendritic cell tumor on review based on expression of a panel of immunohistochemical markers (original magnification x400).

Table 2 - Reported rates of significant disagreement in surgical pathology between original and second opinion review diagnosis in different organs.

Organ/anatomic site	Range of significant disagreement
Global[1,30-32]	0.26 - 6
Lymph node[1,33,34]	1.1 - 27.3
Skin[1,35,36]	1.4 - 2.9
Soft tissue[31,37,38]	2.9 - 25
Lung[31]	3.4
Breast[1,39]	1.4-3
Prostate[31,40,41]	0.5 - 10
Kidney and bladder[31]	5.3
Head and neck[42]	7.0
Thyroid[42,43]	7.5
Gastrointestinal-liver[1,31,44]	1.2 - 7.5
Gynecologic[31]	11.5
Bone[31]	11.1

positive cells admixed with MPO+/CD68+ histiocytes. No classic Reed-Sternberg cells or variants could be seen in the case that has been initially called Hodgkin's lymphoma. In one case there were areas with numerous immunoblastic proliferation, which represent pure proliferative stage of KFD, and this diagnosis was supported by polymerase chain reaction (PCR) for T-cell receptor (TCR) gene rearrangement, which ruled out clonality.

Two of the patients were diagnosed on revision as progressive transformation of germinal center (PTGC). One case was initially called lymphocytes-predominant Hodgkin's lymphoma and the second was initially labeled as partial involvement by follicular lymphoma. In both cases, there was a partial involvement of the node by the process with remaining reactive follicles in the background. No popcorn-type, lymphocytic and histiocytic (L&H) cells could be demonstrated morphologically or by immunohistochemistry which ruled out NLPH. In the second patient, the differentiation from follicular lymphoma was straightforward morphologically. Progressive transformation of germinal center is a benign condition of unknown etiology that does not need any therapeutic intervention; however, clinical follow-up is required for those patients because of the risk of future progression to lymphoma.

Two patients were diagnosed as granulocytic sarcoma (GS) on revision. An important clue in both cases was the absence of expression of immunohistochemistry markers for both B-cells and T-cells. Both samples expressed myeloperoxidase, lysozyme, CD34 and CD117. Immunohistochemistry for myeloid markers was very important for identifying myeloid origin and confirming the diagnosis. In general, the diagnosis of GS requires a high index of suspicion. Granulocytic sarcoma is very often misdiagnosed as a malignant lymphoma, which leads to delayed treatment and a poor outcome.[4-10] Therefore, accurate diagnosis and distinction from lymphoma is very crucial. Yamauchi et al[11] found that 35 patients out of 72 (47%) of GS have initially been misdiagnosed, and the misdiagnosis was most often malignant lymphoma.[11] The 2 cases in our study occurred in duodenum and in the breast. Breast is considered among the preferential sites of GS; however, duodenum is an extremely rare site for this tumor.[11-15] One patient was diagnosed initially as T-cell lymphoma of spleen. He was a young adult male who presented with ruptured spleen. The patient re-diagnosed as benign reactive lymphoid proliferation and infectious mononucleosis was suggested. Polymerase chain reaction for TCR revealed a polyclonal pattern. IMN is one of the mimics of lymphoma.[16-18] Lymphoid tissues are rarely biopsied in IMN patients unless the clinical course is atypical, which may bring lymphoma into the differential diagnosis.[19] Ruptured spleen is not an uncommon presentation in infectious mononucleosis.[20,21] One patient was initially diagnosed as large cell lymphoma and review of the specimen revealed a tumor that is composed of mixture of epitheloid, poleomorphic and spindle cells with an immunohistochemical profile that shows; CD45+, CD117-, Fascin+,CD2-, CD3-, CD4+, CD5-, CD7-, Langerin-, CD1a-, CD21-, CD30-, MSA-, Vimentin+, Pankeratin-, Desmin-, CD20-, CD123-, CD68+, S100+, Lysozyme+, CD23- and CD11c+. Based on this immunohistochemical profile, a diagnosis of interdigitating dendritic cell tumor was made. This tumor is classically negative for B- and T-cell markers.[22-25] Immunohistochemistry study is crucial for the diagnosis. Dendritic cell tumor are commonly misdiagnosed as other neoplasms, more commonly sarcoma and lymphoma.[26-29] Approximately one-third of these cases were misdiagnosed at initial evaluation mainly because the possibility of DCT tumor was not considered.[28]

Two patients were initially misdiagnosed as lymphoma and re-diagnosed as Castleman's disease (CD) on review. One patient initially labeled as angioimmunoblastic T-cell lymphoma (AITL) and the other diagnosed as follicular lymphoma. The first

patient was re-diagnosed as multicentric CD, mixed plasma cell and hyaline vascular type. In this case, the morphological features which favored the CD diagnosis included hyalinized vessels that penetrated atretic follicles, follicular dendritic cells showed concentric layers within atretic follicles, interfollicular areas that contained predominantly plasma cells and most importantly, was the absence of morphologically malignant cells which ruled out AITL. In addition, immunohistochemistry staining for Human Herpes Virus-8 was strongly positive which confirmed HHV-8 positive CD. The second case was a straightforward CD, hyalinized vascular type. Probably the presence of some nodules that contained small germinal centers resulted in the difficulty in recognizing this disease initially.

Two patients were diagnosed with follicular lymphoma by the originating pathologists and were diagnosed as reactive follicular lymphoid hyperplasia on second opinion. The patients have been referred from the same laboratory. In one patient, the review diagnosis was straightforward based on the morphological features that were typical for reactive follicles; however, the fixation and poor cellular preservation interfered with optimal assessment and probably this technical issue was a factor in the misdiagnosis. The second patient was initially labeled as follicular lymphoma based on positive bcl-2 staining that was carried out and interpreted in the original laboratory. However, repeated bcl-2 staining was clearly negative in our institution which confirmed the morphologically reactive looking lymph node. In 3 patients, the diagnoses were changed, from lymphoma to atypical interfollicular lymphoid proliferation, favor reactive. Re-excision of another lymph node in one patient confirmed a reactive condition. Clinical follow-up of other patient was consistent with reactive process. The remaining patients were diagnosed as different types of non-hematolymphoid lesions on review. These included thymoma, gastric poorly differentiated carcinoma, anaplastic thyroid carcinoma, high-grade uterine sarcoma, melanoma and Hashimoto's thyroiditis. The diagnosis in those patients was dependent on morphological features and a panel of appropriate immunohistochemistry staining. On the other hand, in 5 patients the diagnoses were changed from benign or non-diagnostic to lymphoma on the review. One patient was a child who presented to our hospital with mediastinal mass and found to have history of tonsillectomy one month before that was reported as reactive follicular hyperplasia at another institution. Review of the tonsillectomy specimen revealed lymphoblastic lymphoma. Two cases were initially misdiagnosed as tuberculosis, one as reactive and one as non-diagnostic.

In many of the cases, the second opinion diagnosis was based on ancillary tests, particularly a panel of immunohistochemistry stains. In 3 cases, molecular genetic studies were very important to confirm the diagnosis. In 3 cases, the review diagnoses were supported further by an expert opinion from Mayo clinic that concurred with the review diagnoses. Major errors or discrepancies in surgical pathology are those, which have a significant impact on patient care. In the literature, rates of major diagnostic discrepancies reported in studies of second opinion pathology vary substantially. The major discordant rate in surgical pathology between original diagnosis and second opinion diagnosis ranged from 0.26-6% for all kinds of surgical specimens and reach up to 27.3% in some subspecialty or organ specific studies.[30,31-44] Summaries of a number of recent previous studies with respect to major errors in surgical pathology are presented in **Table 2**. The results may vary because review of surgical pathology material is different if it was carried out for a referral prior to therapy or a second opinion versus an in-house self-audit. Major diagnostic revision for lymphoma was found to be in the range between 1.1 and 27.3.[1,33,34] The Pathology Panel for Lymphoma Clinical Studies found that in 16.7% of Hodgkin's lymphoma cases and 27.3% of non-Hodgkin's lymphoma cases, there were major disagreements in the diagnosis provided by the panel pathologists in comparison with that of the submitting pathologists.

The current study demonstrates that second opinion pathology is beneficial for patient care and can reduce the frequency of inappropriate chemotherapy or radiotherapy; thus, second opinion review of outside surgical pathology material for lymphomas is recommended to maximize the discovery of clinically relevant major disagreements. Stringent adherence to institution's second opinion policy is an important quality assurance measure in surgical pathology. In institutions where there is more than one pathologist available, it is advisable to have a policy for intradepartmental consultation for primary diagnosis of lymphoma. It is also highly encouraged that an immunohistochemistry laboratory with a comprehensive panel of antibodies needed for the diagnosis of hematopoietic malignancy is available in any hospital where oncology cases are

referred. Those hospitals should also have their own molecular laboratory or to have an access to molecular genetics services through arrangement with specialized laboratories. It is also advisable for tertiary centers involved in the management of lymphoma to have collaboration with international experts for consultation on very difficult or very rare cases as a third opinion.

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