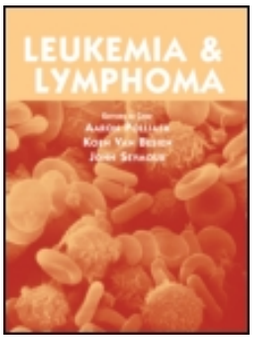

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COMMENTARY

Central review of lymphoma diagnosis: still a prerequisite for best patient care in 2014?

Martina Rudelius & Andreas Rosenwald

Institute of Pathology, University of Würzburg and Clinical Cancer Center Mainfranken, Germany

It has been recognized for a long time that the diagnosis of lymphoma is challenging for most practicing pathologists, due to the clinical rarity and morphological overlap of individual subtypes. However, the correct lymphoma diagnosis is essential for the appropriate management of the patient, as therapy varies significantly between specific subtypes.

In most countries, centralized pathology review for the diagnosis of lymphoma is not yet implemented on a routine basis by the respective health care systems. However, it has become more widely accepted for the inclusion of patients with lymphoma into clinical trials, as for example within the lymphoma task force and pathology reference center established by the National Cancer Institute [1] or a centralized expert review system in the United Kingdom, as recommended by the "Improving outcomes in haematological cancers" guidance manual, where all lymphoma diagnoses are reviewed by a panel of experienced pathologists.

This differs from the introduction of a centralized review system in Germany established in the 1990s by the Deutsche Krebshilfe, where an expert second opinion is obtained and difficult routine cases are submitted on a regular basis.

Before the introduction of the World Health Organization (WHO) classification [2], discrepancies between referral and review diagnoses accounted for up to 43% of cases [3,4]. Thereafter, the consistency of lymphoma diagnosis has much improved, as this worldwide accepted approach of classification seems to be more practicable also for the general community of pathologists.

In this issue of ***Leukemia and Lymphoma***, two studies suggest that also in the era of the WHO lymphoma classification system a central review system is beneficial for patient management. In East Netherlands [5], a system comparable to the centralized expert review system in the UK was implemented a while ago, and all primary diagnoses of malignant lymphoma were reviewed by an expert panel of hematopathologists. Similarly, in Taiwan [6], a consultation program was conducted, where general pathologists could submit difficult cases on a voluntary basis. Major discrepancies were defined as cases where the change of diagnosis altered patient management.

Discordance rates of cases with major discrepancies were significantly different, with a rate of 14% in the Dutch study and a rate of 55% in the Taiwanese study. Whereas 14% is in the range of reported discrepancies [7–9], 55% seems to be extremely high, and compares to rates before introduction of the WHO classification system. Before the introduction of the Revised European–American Lymphoma (REAL) and WHO classification, the diagnosis of lymphoma was mainly based on morphological features of the tumor. The WHO has emphasized the additional use of ancillary methods such as immunohistochemistry and molecular pathology, and defined disease entities taking the morphology, immunophenotype, molecular as well as genetic features, and clinical presentation into account. This approach has been reinforced by the update of the WHO classification in 2008. Clearly, ancillary methods are more accessible for the general community of pathologists in The Netherlands compared to the situation in Taiwan, which could explain in part the difference in discordance rates between the two groups. However, probably even more important is that, in Taiwan, cases could be submitted for review without a definite diagnosis by the primary pathologist, and these cases accounted for 52% of cases with major discrepancy.

Interestingly, the overall discordance rate in The Netherlands decreased from 14% in 2000–2001 to 9% in 2005–2006, which could be attributed to a learning curve of primary pathologists by regular review and discussion of the cases in the expert panel. Therefore, a reviewing system where general pathologists are trained (two-step system) should be preferred over a direct submission of cases to an expert panel, even though it is more time consuming.

Five years after the update of the WHO classification, the reproducibility of lymphoma diagnosis has improved; however, discordance rates are still relatively high. As pointed out by Strobbe and colleagues, even though the accuracy of diagnosis in some entities has improved with the use of ancillary methods, such as for example the diagnosis of

Correspondence: Martina Rudelius, Institute of Pathology, University of Würzburg, Germany. E-mail: Martina.Rudelius@uni-wuerzburg.de

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mantle cell lymphoma with the use of cyclin D1 immunhistochemistry, there are still some entities where the reproducibility between the primary and expert pathologists is relatively low. In our own experience as a large reference center for malignant lymphomas in Germany, the diagnosis of marginal zone lymphomas and, especially, T-cell lymphomas still represents a major challenge for many primary pathologists.

In conclusion, given the risk of misdiagnosis and false clinical management of the patient with lymphoma, central review systems have proved to be valuable for the patient, clinician and pathologist. Moreover, good arguments can also be made that this approach is cost-effective, since (wrong) treatment of patients with lymphoma is expensive compared to additional costs caused by an expert review. Thus, also in 2014, the gold standard for lymphoma diagnosis should be a multidisciplinary approach that includes review of difficult cases by experienced hematopathologists.

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