The real risk of secondary non-Hodgkin lymphoma following classical Hodgkin lymphoma

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Classical Hodgkin lymphoma (CHL) is a B-cell lineage lymphoid malignancy. The majority of the patients are diagnosed between 15 and 30 years of age, followed by another peak in adults aged ≥55 years. Most cases of CHL are curable by modern treatments.[1] However, therapeutic modalities such as radiotherapy and chemotherapy used to achieve this high rate of cure have side effects in the long term, especially in young patients.[2] The leading causes of long-term toxicity caused by therapy include cardiovascular disease and secondary malignancies such as breast cancer and therapy-related myeloid neoplasms. In addition, case control and registry studies suggest that CHL patients may have familial predisposition and germline susceptibility to develop additional lymphoid malignancies.[3] Previous studies, including a large cohort study with long-term and complete follow-up, showed that the risk of developing a secondary non-Hodgkin lymphoma (NHL) was increased significantly up to 13-fold in CHL patients compared to that in the general population.[4]

In this issue of *Haematologica*, Boot *et al.* re-assess this risk based on an in-depth pathology review of a nationwide cohort of patients with CHL in the Netherlands.[5] The study was designed to review the accuracy of pathological diagnosis of NHL following CHL. The cohort was restricted to 2,669 patients with CHL diagnosed between 2006-2013 for whom the initial diagnosis of CHL could be confirmed by review of pathology reports. Fifty-four of these 2,669 cases of CHL (2%) had a subsequent diagnosis of NHL. The expert pathology review was restricted to the 54 cases for which both the original CHL diagnosis and subsequent NHL diagnosis were available.

The review confirmed the CHL diagnosis and subsequent NHL in 25 cases. Interestingly, six of the cases were biologically, and very likely clonally, related to the original CHL such as primary mediastinal large B-cell lymphoma and mediastinal gray zone lymphoma, suggesting that these would be best considered relapses of the same neoplastic disorder rather that unrelated secondary neoplasms.[6] Eighteen of the 19 remaining cases were different histologies of NHL, presumably representing true secondary malignancies.

In 29 out of 54 cases, the initial diagnosis of CHL was not confirmed. The wrong diagnoses included common mimics of CHL such as Epstein-Barr virus (EBV)-positive Hodgkin-like cells frequently seen in peripheral T-cell lymphomas and EBV-associated large B-cell lymphomas, CD30-expressing T-cell lineage neoplasms such as anaplastic large cell lymphoma, and CD30-positive immunoblasts which can be seen in reactive/inflammatory conditions. As a result of revisions of original pathological diagnoses, the authors calculated that, in the cohort they studied, the standardized incidence ratio of developing NHL after CHL was significantly lower, at 3.61 (95% confidence interval: 2.29-5.42; *P*=0.002) compared to 7.79 (95% confidence interval: 5.78-10.3) based on original data.

The study highlights the significance of high quality pathology data and expert review in large scale epidemiological studies, especially in the context of secondary malignancies. As such studies have important implications for surveillance guidelines for patients with a prior cancer diagnosis, rigorous methods to address the quality of pathology data are essential.

Secondly, the findings stress the importance of obtaining biopsies for pathology work-up at relapse in CHL, as these may reveal not only phenotypic shift, as exemplified by cases diagnosed as primary mediastinal large B-cell lymphoma or gray zone lymphoma, but also other distinct histologies which may become apparent in relapse biopsies, such as T-cell lymphomas or EBV-driven B-cell lymphomas. The authors point out that the misdiagnoses were associated with a number of clinicopathological features including advanced age, generalized lymphadenopathy at presentation (stage III/IV disease) and the presence of EBV infection. Such features, in suspected relapse of CHL, should prompt comprehensive work-up with histopathological examination to address the diagnostic pitfalls highlighted in this study.

Some of important issues remain unanswered by the study. No expert review of the cases diagnosed as CHL (n=2,615)

without a subsequent diagnosis of NHL was performed. Of these, 289 cases relapsed with CHL. The relapsed CHL cases showed clinicopathological features similar to those of patients misdiagnosed as CHL but actually represented other NHL. Although the rate of misdiagnosis of CHL is low, around 6-7%,[7] it is likely that, given the size of the cohort, 150 cases may have been misdiagnosed without expert review. Therefore, it is difficult to establish a more accurate estimate of the incidence of NHL in CHL patients without broader pathology review either focusing on relapsed cases, or ideally, all cases diagnosed as CHL. In a small subset of the cases additional material for review and additional work-up was not available; the expert review was restricted to pathology report review, which may undermine the findings. With the caveats above, Boot *et al.* make an important contribution to the field not only by showing the importance of thorough pathology assessment for epidemiological studies of lymphoid neoplasms but also by emphasizing the pitfalls in the diagnosis of CHL and their clinical significance.

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