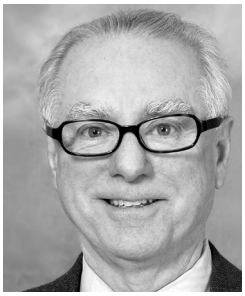
Editorial

Rheumatoid Arthritis and Lymphoma: Risky Business for B Cells



Convincing evidence indicates that patients with rheumatoid arthritis (RA) have about a 2-fold increased risk of developing lymphoma[1-4]. The results of a large recent case-control study show that the risk of lymphoma is highly correlated with RA disease activity and not with specific therapy[5]. This editorial will discuss the context of these findings, and the implications for management of RA.

Over 90% of lymphomas are of B cell origin despite a similar frequency of B and T cells in humans. Advances in understanding basic pathogenesis of B cell development and proliferation provide insights into how lymphomas develop. The processes that enable B cells to respond and proliferate to specific antigens increase the risk of developing malignancy[6]. The central thesis in lymphoma development holds that chronic stimulation of B cells by antigen or by virus, coupled with local inflammation, and immunosuppression-induced decreased surveillance by tumor-infiltrating immune cells, both T and non-T cells, lead to a heightened risk of malignant B cell lymphomas.

A critical role in normal B cell development is played by the B cell receptor for antigen, a cell-surface structure composed of heavy and light-chain immunoglobulins. Normal B cell differentiation takes place in distinct stages based upon differentiation of this receptor. Early B cells leave the bone marrow when their B cell receptor rearranges to become functional. These naive but mature B cells then migrate to lymph node germinal centers. Here, upon exposure to antigen and under the influence of T cells, these B cells undergo vigorous clonal proliferation. The B cell receptor genes undergo editing in a process that involves somatic hypermutation and class-switch recombination, allowing B cells to refine specificity of the B cell receptor. However, this genetic editing also leads to increased risk of B cell transformation.

What mechanisms lead to transformation and emergence of a B cell lymphoma? Although transformation to a malignant clone is a multistep process, a hallmark of B cell non-Hodgkin's lymphoma (NHL), seen in up to 90% of cases, is the presence of a chromosomal translocation between an immunoglobulin (Ig) and a proto-oncogene gene locus, particularly BCL-6[7]. The process of Ig somatic hypermutation in normal B cells, which involves cleavage and rearrangement of Ig genes, causes DNA strand breaks that affect other, non-Ig gene partners, primarily BCL-6 and the tumor suppressor gene CD95. The result is control of the oncogene by the active Ig gene, leading to deregulated, constitutive expression of the oncogene and/or other tumor-regulating genes, with uncontrolled proliferation[6]. Class-switching and somatic hypermutation occur in germinal center B cells and do not occur in T cells, which may explain why germinal center B cells are more prone to undergo malignant transformation compared to T cells. Additional transforming events may affect other non-Ig gene targets, also likely as a result of somatic hypermutation in germinal center B cells, causing mutations in other oncogenes (BCL-2, c-myc) and tumor suppressor genes (TP53), genomic amplifications, and translocations not involving Ig loci.

Nearly all B cell NHL express the B cell receptor, suggesting that chronic antigen stimulation plays a central role in their emergence[6]. An increased risk of lymphoma is found among individuals with several chronic inflammatory conditions, including RA, persistent infections, or immunodeficiency states, which may account for the 2-fold rise in lymphoma incidence over the past several decades[8]. The failure of the antigenic stimulus to subside, as occurs with persistent infections or with endogenous autoantigens, can increase the chance of B cell transformation as described above.

Very little is known regarding the nature of the antigens inciting lymphomas, although Martin, *et al* found that Ig products of the neoplastic B cells were rheumatoid factors in salivary gland lymphomas of patients with Sjögren's syndrome[9]. Other examples of chronic stimulation by antigens leading to lymphoma include hepatitis C[10] and *Helicobacter pylori*[11].

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Viral infection, especially the ubiquitous Epstein-Barr virus (EBV), may also cause transformation of B cells. Germinal center B cells appear to be particularly susceptible to EBV transformation[12]. EBV can "substitute" for an intact B cell receptor in leading to B cell transformation, preventing apoptosis of such B cell receptor-negative B cells[12]. EBV plays a major role in lymphomas arising in the presence of immunosuppression, whether iatrogenic, as follows organ transplants, inherited, or acquired, with 50%–80% being EBV-infected[13]. Common features of these disorders are chronic infection, both with EBV and with other agents, and dysregulation of the cell-mediated immune system, with loss of malignant cell surveillance by T cells playing a major role. Infection by EBV in these settings appears to be necessary but not sufficient for development of lymphoma: progression to lymphoma requires additional genetic transformation events as described above.

Another contributor to the development of B cell lymphoma relates to the local microenvironment of the tumor. Recent gene profiling studies describe that the behavior of lymphomas relates to the molecular signature of the nonmalignant, tumor-infiltrating cells, including T cells and monocytes, indicating that the immune response to the malignant B cells plays a major role in prognosis[14]. Intratumoral regulatory T cells may have both direct and indirect effects on growth of malignant lymphoma B cells[15], but surprisingly little is known about how T cells provide immunosurveillance against B cell lymphomas.

In summary, emergence of B cell lymphomas depends on transforming events, on survival signals from the B cell receptor plus antigen or from virus, and on local microenvironment conditions. The conditions in RA that relate to lymphoma development need to be understood in this context.

As noted, patients with RA have about a 2-fold increased risk of developing lymphoma[1-4]. Although some studies have examined the relationship between therapeutic agents used to treat RA and the development of lymphoma, the findings have been so confounded by the effects of disease activity that few conclusions can be made regarding a causal relationship between therapy and development of lymphoma[3,4].

A recent case-control study by Baecklund, *et al* of nearly 400 Swedish RA patients and controls examined the role of disease activity in the risk of developing lymphoma[5]. The results showed that risk of lymphoma was highly correlated with RA disease activity and not with specific therapy[5]. The study by Hoshida, *et al* in this issue of *The Journal*, which examines the clinical pathologic features of 76 cases of RA lymphoma in Japan, provides supplementary information regarding histologic type, presence of EBV, association with methotrexate (MTX) treatment, and response to treatment[16]. Further, Hoshida, *et al* compare findings in the RA lymphoma cases with findings in lymphoma arising sporadically in Japan, and with posttransplant lymphoma cases reported in Japan.

In RA, the most common form of lymphoma is a diffuse large B cell lymphoma (DLBCL)[5,16,17], which is thought to arise from normal antigen-exposed B cells in lymphoid germinal centers[6]. Consistent with these findings, Hoshida, *et al* found that DLBCL was the most common subtype of NHL, occurring in 58% of NHL in this series, significantly higher than in the sporadic NHL cases (43%). Prior treatment with MTX did not influence the percentage of DLBCL in RA or the prevalence of EBV in the tumor. However, EBV was more common in the RA-associated DLBCL (14%) compared to the sporadic DLBCL (4%), suggesting that EBV could account for some of the excess risk of DLBCL in RA. The prevalence of DLBCL and infection with EBV in 3 published reports of RA lymphomas is shown in Table 1. These results indicate that, overall, EBV plays an important but not a central role in the pathogenesis of lymphomas in RA; the increase in DLBCL above background could in part be EBV-related.

The potential role of MTX in inducing EBV-related lymphomas in patients with RA has been of considerable interest[18]. EBV-specific T cells from patients with RA were reported to have reduced ability to control outgrowth of EBV-infected B cells *in vitro*[19], although no studies have examined the effect of MTX on such T cells. More recently, Feng, *et al* reported that MTX activated release of infectious EBV from latently infected cell lines *in vitro* and was associated with activation of viral promoter genes[20]. Further, patients with RA treated with MTX had higher EBV loads in their blood compared with RA patients not receiving MTX[20]. Multiple case reports document regression of EBV-associated lymphomas in RA patients in whom MTX was stopped[21]. Kamel, *et al* found in a case-control study of NHL in RA patients not exposed to MTX that the prevalence of tumors associated with EBV was low, 2%[22].

Franklin, *et al* found an increased risk in RA patients of NHL associated with MTX, but the effect was confounded by the coexistence of active disease, and no relationship to EBV status of lymphomas was examined[4]. Other studies, however, have not found an increased risk of NHL in MTX-treated RA patients[23]. Mariette, *et al* found an increased risk of Hodgkin's lymphoma, but not NHL, in a prospective 3-year study of MTX-treated RA patients in France[17].

Based on such considerations, this author predicted in a previous editorial that an increased frequency of EBV-asso-

Table 1. Comparison of diffuse large B cell lymphoma (DLBCL) and Epstein-Barr virus (EBV) prevalence in non-Hodgkin's lymphoma (NHL).

Study	RA	Percentage of NHL	EBV, No. positive/ total no. (% positive)
Hoshida[16]	Yes	57.9	6/44 (13.6)
Baecklund[5]	Yes	53	19/160 (12)
Mariette[17]	Yes	67	2/12 (16)
Hoshida[16]	No	42.7	2/50 (4)

ciated NHL would be found when MTX versus non-MTX treatments were compared in a larger series of RA-associated lymphomas[24]. The studies of Hoshida, Baecklund, and Mariette, *et al*[5,16,17] show that this is not the case: MTX treatment has no influence on the prevalence of EBV in RA-associated NHL in general and in DLBCL in particular.

Nevertheless, Hoshida, *et al* found that stopping MTX in the 48 patients who developed lymphoma resulted in regression in 11, of whom over half were EBV-positive. Similar findings were reported by others[17,25]. These findings suggest that MTX can influence local tumor immunity, retarding lymphoma progression. While the effect is not dependent on the presence of EBV, tumor regression is more common in EBV-positive lymphomas. The findings do not mean that MTX predisposes to lymphoma development. Whether the antiinflammatory properties of MTX could account for these findings is not known[26].

Besides increased stimulation of B cells to explain the relation between disease activity in RA and the risk of lymphoma, are there potential effects imposed on RA T cells by active disease? Of note are the studies by Wilder and colleagues showing that a subset of RA patients with active disease were anergic, an effect on T cells that was reversed by lymphopheresis[27]. Weyand and Goronzy have shown that RA T cells have evidence of premature aging, shown by erosion of telomeres and a restricted T cell diversity[28]. Additional studies are needed to unravel the role of regulatory T cells in RA and their potential effects on lymphoma development[29].

In summary, consistent with the model of development of B cell lymphomas, patients with RA have an increased risk of developing lymphoma related to disease activity, an effect likely operating at both the B and T cell level. The finding of an increased risk of developing lymphoma is consistent with the role of B cell activation in contributing to RA disease activity. The benefits of B cell-specific therapy in RA[30] also support this contention. The contribution of drug therapy, which may involve some form of immunosuppression, to risk of lymphoma development is confounded by the treatment of patients with active disease. Since lymphoma risk appears to be independent of the use of any specific treatment, it is likely that effective treatment will reduce this risk.

What are the implications of these findings for treating RA? We need to consider strategies to minimize disease burden and duration of therapy. It is likely that lymphoma risk shares other features of comorbidities in RA such as work disability, increased risk of cardiovascular disease, and reduced lifespan, all of which appear related to disease severity and duration[31]. These findings lend increased urgency to control of disease activity early and on a sustained basis. Of special interest are recent preliminary studies with tumor necrosis factor-blocking therapy in early RA, which raise the possibility of a sustained remission without continued therapy[32,33].

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