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Review

Lymphoma development in patients with autoimmune and inflammatory disorders – What are the driving forces?

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ABSTRACT

For decades, it has been known that patients with certain autoimmune and inflammatory disorders, such as rheumatoid arthritis (RA) and primary Sjögren's syndrome (pSS), have an increased risk of developing malignant lymphoma. Although the clinico-biological reasons for this association remain largely unknown, our knowledge has improved and new insights have been obtained. First, the direct link between autoimmunity and lymphomagenesis has been strengthened by large epidemiological studies showing a consistent risk increase of lymphoma associated with certain autoimmune/inflammatory conditions in independent cohorts from different countries. Second, a number of local and systemic disease-related risk factors in these diseases have been repeatedly linked to lymphoma development, with the prime examples being disease severity and the degree of inflammatory activity. Considering the key role of B- and T-cell activation in the pathogenesis of both autoimmunity and lymphoma, it is perhaps not surprising that longstanding chronic inflammation and/or antigen stimulation have emerged as major predisposing factors of lymphoma in patients with active autoimmune disease. Finally, increasing evidence suggests that lymphomas associated with autoimmunity constitute a different spectrum of entities compared to lymphomas arising in patients without any known autoimmune or inflammatory conditions, pointing to a different pathobiology. In this review, we summarize the recent literature that supports a direct or indirect link between immune-mediated disease and lymphoma and describe the characteristics of lymphomas developing in the different diseases. We also discuss molecular, genetic and microenvironmental factors that may come into play in the pathobiology of these disorders.

1. Introduction

The longstanding recognition of increased lymphoma risk in patients with some of the most common autoimmune and inflammatory conditions has been the strongest argument for a direct association between these diseases and lymphoma development [1–3]. Today, it is well established that the risk of developing lymphoma is increased in patients with autoimmune or inflammatory conditions such as rheumatoid arthritis (RA), primary Sjögren's syndrome (pSS), systemic lupus erythematosus (SLE), celiac disease, dermatitis herpetiformis, and Hashimoto's thyroiditis. However, for other autoimmune/inflammatory diseases the data is either (i) conflicting (e.g. as in psoriasis, Crohn's disease and sarcoidosis), (ii) associations with lymphoma have been poorly studied (e.g. in psoriatic arthritis and rare vasculitides), or (iii) no overall increased risk has convincingly been identified (e.g. ulcerative colitis, ankylosing spondylitis and polymyalgia rheumatica) [1–3].

That said, when studying these associations one must bear in mind the large heterogeneity not only within and between the various autoimmune/inflammatory diseases, but also within and between different subtypes of malignant lymphomas. Therefore, an overall lack of association with an inflammatory disease does not preclude an increased risk of lymphoma among subgroups of patients. Indeed, with larger and more detailed studies, data is now emerging which supports the idea that the increased lymphoma risk may be confined to one or two specific lymphoma subtypes and also to subgroups of patients displaying particular features of the immune-mediated disease. The prime example is the strong association between disease intensity in RA and one of the most aggressive lymphoma subtypes, namely diffuse large B-cell lymphoma (DLBCL) [4].

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Table 1
Studies of lymphoma risks in patients with RA, SLE, Sjögren's syndrome and celiac disease published since 2009.[a]

Disease	Country	Study period	RR of lymphoma/SIR (95% confidence interval)	Reference author, year
RA				
	US	1993–2002	OR NHL 1.2 (1.1–1.3)	Anderson, 2009 [120]
	Sweden	1999–2006	RR lymphoma 2.7 (1.8–4.1)	Askling, 2009 [121]
	California, US	1991–2002	RR NHL Men 2.1 (1.7–2.5) Women 1.4 (1.2–1.6)	Parikh-Patel, 2009 [122]
	Sweden	1997–2006	HR lymphoma, first 10 years of RA disease: 1.8 (1.0–3.0)	Hellgren, 2010 [5]
	UK	2002–2009	SIR NHL 3.1(1.8–5.1)	Mercer, 2013 [123]
	Denmark	2000–2008	SIR NHL 2.3 (0.9–5.4)	Dreyer, 2013 [124]
Sjögren				
	US	1993–2002	OR NHL 1.9 (1.5–2.3)	Anderson, 2009 [120]
	China	1990–2005	SIR NHL 48.1 (20.7–94.8)	Zhang, 2010 [125]
	Spain	1988–2008	SIR NHL 15.6 (8.7–28.2)	Solans-Laqué, 2011 [21]
	Taiwan	2000–2008	SIR NHL Men 3.1 (0.6–9.0) Women 7.1 (4.2–10.3)	Weng, 2012 [126]
	Norway	1980–2009	SIR NHL 9.0 (7.1–26.3)	Johnsen, 2013 [127]
	Meta-analysis	11studies 1954–2009	Pooled RR 13.8 (8.5–19.0)	Liang, 2013 [128]
SLE				
	US	1993–2002	OR NHL 1.5 (1.2–1.9)	Anderson, 2009 [120]
	Korea	1997–2007	SIR NHL 15.4 (2.9–37.7)	Kang, 2010 [129]
	Taiwan	1996–2007	SIR lymphoma 7.3 (7.0–7.6)	Chen, 2010 [130]
	Denmark	1951–2006	SIR NHL 5.0 (1.9–13.3)	Dreyer, 2011 [131]
	International (US, Canada, Europe, Korea)	1958–2009	SIR lymphoma 4.1 (3.2–5.0) SIR NHL 4.4 (3.5–5.5) SIR HL 2.3 (0.9–4.7)	Bernatsky, 2013 [132]
Celiac disease				
	Sweden	1965–2004 1975–1984 1985–1994 1995–2004	OR NHL 5.4 (3.6–8.1) OR NHL 13.2 (3.6–48.0) OR NHL 7.9 (3.4–18.5) OR NHL 3.8 (2.3–6.4)	Gao, 2009 [30]
	US	1993–2002	OR NHL 1.5 (0.9–2.5) OR T-cell lymphoma 5.9 (2.4–14)	Anderson, 2009 [120]
	Sweden	1969–2008	SIR NHL 2.8 (2.4–3.4) SIR T-cell NHL 48.0 (15.8–145) SIR B-cell NHL 1.9 (1.3–2.7)	Elfström, 2011 [133]
	Scotland, UK	1970–2004	SIR NHL 5.2 (1.4–13.2)	Grainge, 2012 [134]
	Meta-analysis	8 studies (NHL) 5 studies (T-cell NHL) 1993–2008	OR NHL 2.6 (2.0–3.3) OR T-cell NHL 15.8 (7.8–31.9)	Tio, 2012 [33]
	US	1981–2010	SIR NHL 6.9 (4.2–8.2) SIR DLBCL 5.4 (1.9–10.5) SIR T-cell NHL 22.4 (7.1–46.4)	Leslie, 2012 [135]
	Sweden	1969–2009	SIR NHL 2.8 (2.1–3.7)	Lebwohl, 2013 [26]

DLBCL = diffuse large B cell lymphoma, HL = Hodgkin lymphoma, HR = hazard ratio, NHL = non-Hodgkin lymphoma, OR = odds ratio, RA = rheumatoid arthritis, RR = relative risk, SIR = standardized incidence ratio, SLE = systemic lupus erythematosus.

[a] Studies before 2009 reviewed in [1,2].

Furthermore, it is apparent that the magnitude of the risk estimates varies considerably between studies. One of the reasons behind this diversity is that earlier and smaller studies on selected patients typically reported higher risk estimates compared to more recent, larger and population-based studies [1–3]. Nevertheless, a recurrent finding in rheumatic diseases is that the highest relative risk for lymphoma is associated with pSS, followed by SLE and RA, thus indicating a disease-specific risk profile. Recent estimates of the relative risks in unselected populations appear to be more consistent across studies from Western countries, ranging from about 2 in RA, 3–7 in SLE to 9–16 in pSS compared to a general population (more recent and seminal studies of lymphoma risk in selected autoimmune/inflammatory conditions are summarized in Table 1). In addition, despite improved disease control, it is noteworthy that in Swedish RA patients the average risk for lymphoma (approximately double that of the general population) has remained relatively stable over the last decades [5].

Although strong evidence for an increased risk of lymphoma in certain autoimmune/inflammatory conditions has existed for many years, it was only more recently that we began to identify factors that may act as the driving forces behind lymphomagenesis within this particular setting. In this review, we summarize the disease-related, environmental and genetic risk factors that have been proposed as the potential "drivers" ultimately leading to lymphoma development in patients with autoimmune diseases. In light of the crucial role of B- and T-cell activation in the pathogenesis of both autoimmunity and lymphomas, chronic inflammation and antigen stimulation are especially relevant to discuss as potential determinants for lymphoma development within this setting. Finally, we also review potential leads to the pathobiology provided by studies of clinical and molecular characteristics of the specific lymphoma subtypes that have been associated with each autoimmune/inflammatory condition.