Concise Report

Hodgkin’s lymphoma in systemic lupus erythematosus

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Objective. In systemic lupus erythematosus (SLE), there is a well-documented increased risk of non-Hodgkin’s lymphoma (NHL), but little is known about the risk of Hodgkin’s lymphoma (HL). The purpose of our work was to describe the phenomenon of HL in SLE.

Methods. A multi-site cohort of 9547 SLE subjects was assembled; HL cases were ascertained through cancer registry linkage, and the standardized incidence ratio (SIR) for HL was determined. We also performed a literature search for HL cases in SLE, and compared these with our sample. Finally, we pooled results from our cohort study with two large population-based cohort studies providing SIR estimates for HL in SLE.

Results. Five cases of HL occurred in our SLE cohort during the observation interval, for an SIR of 2.4 (95% CI 0.8, 5.5). The literature review documented 13 HL case reports developing in patients with SLE. A pooled analysis combining our data with the other large cohort studies yielded a standardized incidence ratio of 3.16 (95% CI, 1.63–5.51) for HL in SLE.

Conclusions. Data suggest that risk in SLE is increased not only for NHL, but also for other malignancies arising from B-lymphocytes, including HL.

KEY WORDS: Hodgkin’s lymphoma, Systemic lupus erythematosus.

Interest is quickly growing regarding the increased risk of malignancies in autoimmune conditions such as systemic lupus erythematosus (SLE) [1–3]. We recently completed a multi-site international cohort study that calculated standardized incidence ratios (SIRs) for cancer in SLE vs the general population [3]. In that study, the most dramatic increased risk of cancer was seen in haematological malignancies, with an SIR of 2.8 [95% confidence interval (CI) 2.1, 3.5]. The data suggested that most types of haematological malignancies were increased, although the most precise estimates were produced for non-Hodgkin’s lymphoma (NHL), since this is by far the most frequent haematological malignancy (both in the general population and in autoimmune rheumatic conditions).

Some have suggested that malignancy risk in SLE is increased also for other haematological malignancies, particularly those arising from B-lymphocytes. For example, case reports of Hodgkin’s lymphoma (HL) in SLE patients have been noted in the literature for many decades. To date, clear summary data are lacking regarding the magnitude of risk, the distribution of pertinent demographic factors, and the outcomes in the HL cases that arise in SLE. We, therefore, provide in this concise report the details of the HL cases in our multi-centre SLE cohort, in conjunction with a summary of literature published on HL in SLE, both from case reports and in two other very large recent cohort studies.

Materials and methods

We assembled a multi-site international cohort study involving 23 clinical centres in Canada, the US, the UK (England and Scotland), Sweden, Iceland and Korea [3]. The criteria for entry were that patients had definite, clinical SLE confirmed by a rheumatologist or other lupus specialist; the majority (>90%) of the subjects met American College of Rheumatology classification criteria for SLE. The calendar time spanned 1958–2000, but most of the patient-years of observation were from 1970 onward.

Data were available regarding patient birth date and sex, dates of SLE diagnosis and cohort entry, and vital status. HL cases occurring after SLE diagnosis were ascertained by regional cancer registry linkage. Vital statistics linkages were performed for patients deceased or lost to follow-up, in the US cohorts with the National Death Index, and for the non-US cohorts with regional vital statistics registries. To calculate person-years of follow-up, we subtracted the later of two entry dates (beginning of cancer registry observation interval or first visit to the respective SLE clinic) from the earlier of two exit dates (end date of tumour registry data or death). SIRs were obtained by dividing the observed number of cancers by the expected number. The expected number of cancers was obtained by applying age, sex and calendar-year appropriate general population cancer rates (provided by the relevant regional cancer registries) to the person-years of follow-up in the SLE cohort.

We summarize demographics and survival for all HL cases occurring within our observation interval. We then discuss the findings in conjunction with a synopsis of HL cases previously reported in individuals with established SLE. We considered both case reports found in a computerized search of published medical literature, and the HL cases arising from the two large population-based SLE cohort studies that have been published to date.

For the computerized search, we used the text-based search and retrieval system of the National Center for Biotechnology Information to search the 16 million citations from MEDLINE and other life science journals for biomedical articles. We initially searched back to the 1950s using the terms ‘Hodgkin’ (or Hodgkin’s) AND ‘SLE’ (or lupus). Initial selection criteria for review of the case reports were that summaries of the articles were available in English. After reviewing the titles and abstracts, we eliminated case reports indicating that the lymphoma had occurred prior to the SLE diagnosis. We examined the articles from the remaining citations and included those case reports of a HL occurring after an established diagnosis of SLE. Individuals with discoid or drug-induced lupus were not considered.

Of the cohort studies of cancer in SLE that have been published recently, all but two are from clinical centres that participated in...
our multi-centre study. The remaining two are large population-based SLE cohort studies [1, 2]. We thus completed a pooled analysis combining our findings [3] with those of these other two studies [1, 2] by summing the total number of observed and expected cases of HL in the three studies, dividing the observed number of cancers by the expected number, and calculating 95% CIs using methods described [4] for Poisson parameters. In addition to simple pooling, we also fit a random effects hierarchical model, using the Gibbs sampler as implemented in WinBUGS 1.4 software to estimate the model parameters, with 95% credible intervals [5]. At the first level of the hierarchical model, the number of observed HL cancers within each study \(i\) was assumed to follow a Poisson distribution, with mean \(\theta_i = \lambda_i t_i\), where \(\lambda_i\) is the HL cancer rate for study \(i\), and \(t_i\) is the total person-years for study \(i\). The second level of the model specifies a gamma distribution \(\lambda_i \sim \text{gamma} (\alpha, \beta)\) for the study mean. Diffuse prior distributions were used for the gamma priors, \(\alpha \sim \text{exp} (1.0)\) and \(\beta \sim \text{gamma} (0.1,1)\) so that the data would dominate the posterior distribution [6].

Results

Our cohort numbered 9547 subjects, and these individuals were observed for a total of 76,948 patient years [3]. Five cases of HL occurred during the observation interval, for an SIR of 2.4 (95% CI 0.8, 5.5). Two of these cases were male; two individuals were less than 35 years (aged 24 and 28 years) and the remainder age ranged from 56 to 67 years. Only one of the five cases (a female who developed Hodgkin’s at an age of 56) had died (3 years after Hodgkin’s diagnosis) by the end of the observation interval.

Our literature review (Table 1) of case reports yielded 13 reported cases of HL developing after SLE, which occurred over the period from 1984 to 2005 [7–17]. Seven of these involved female patients. Of these reported cases, two of the affected individuals were white, two were black, one was Hispanic, and in the remainder race/ethnicity was not known. The age at time of Hodgkin’s diagnosis ranged from 15 to 58 years; six of the cases were aged 40 years or younger, two were between the ages of 41 and 50 years, and five were greater than 51 years of age. Of the 13 cases, death occurred rapidly in four patients.

The two large published population-based cohort studies that have examined lymphoma occurrence in SLE were an analysis of 1585 patients in Denmark, published in 1997 [1] and a more recent study of 5715 patients in Sweden, published in 2002 [2]. The SIRs for these studies, along with 95% CIs, are presented in Fig. 1. The pooled analysis combining our findings [3] with those of these other two studies [1, 2] provided an SIR estimate for HL in SLE of 3.16 (95% CI 1.63, 5.51). The random effects model estimate was very similar (SIR 3.08, 95% CI 1.44, 5.35).

Discussion

Despite the fact that we had relatively few cases in our multi-centre international cohort study, our data seemed to follow the bimodal incidence curve seen in the general population.

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**Table 1. Cases of HL reported in the literature**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Sex</th>
<th>Age</th>
<th>SLE duration</th>
<th>Drug exposure prior to HL</th>
<th>HL treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Goodwin [7]</td>
<td>M</td>
<td>23</td>
<td>12 years</td>
<td>Prednisolone, azathioprine</td>
<td>Mechlorethamine, vincristine, procarbazine, prednisolone</td>
<td>Remission</td>
</tr>
<tr>
<td>2 Efremidis et al. [8]</td>
<td>F</td>
<td>15</td>
<td>11 months</td>
<td>Prednisolone</td>
<td>Nitrogen mustard, vincristine, procarbazine, prednisolone</td>
<td>Remission 10 months</td>
</tr>
<tr>
<td>3 Scully et al. [10]</td>
<td>F</td>
<td>58</td>
<td>3 months</td>
<td>Hydroxychloroquine</td>
<td>None</td>
<td>Death at 14 days</td>
</tr>
<tr>
<td>4 Houssiau et al. [11]</td>
<td>Not indicated</td>
<td>23</td>
<td>Simultaneous</td>
<td>Prednisolone</td>
<td>Five courses chlorambucil, vinblastine, procarbazine and prednisolone (Ch1Vpp)</td>
<td>Not indicated</td>
</tr>
<tr>
<td>5 Netto and Shan [9]</td>
<td>M</td>
<td>45</td>
<td>Simultaneous</td>
<td>None</td>
<td>None</td>
<td>HL at autopsy</td>
</tr>
<tr>
<td>6 Bhalla et al. [2]</td>
<td>F</td>
<td>58</td>
<td>10 years</td>
<td>Prednisolone, hydroxychloroquine</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>7 Menon et al. [13]</td>
<td>M</td>
<td>54</td>
<td>Not indicated</td>
<td>Prednisolone</td>
<td>Local radiation</td>
<td>Remission</td>
</tr>
<tr>
<td>8 Rakfal and Deutsch [14]</td>
<td>F</td>
<td>38</td>
<td>8 years</td>
<td>High-dose steroids, IV immunoglobulin</td>
<td>One dose vincristine</td>
<td>Not indicated</td>
</tr>
<tr>
<td>9 Schachna et al. [15]</td>
<td>F</td>
<td>56</td>
<td>3 years</td>
<td>Hydroxychloroquine</td>
<td>Vincristine, etoposide, chlorambucil, prednisolone</td>
<td>Death at 3 months</td>
</tr>
<tr>
<td>10 Merino et al. [16]</td>
<td>M</td>
<td>18</td>
<td>9 years</td>
<td>Prednisolone, azathioprine, hydroxychloroquine</td>
<td>6 cycles of Adriamycin (doxorubicin), bleomycin, vincristine, dacarbazin (ABVD), radiation</td>
<td>Remission</td>
</tr>
<tr>
<td>11 Patel et al. [17]</td>
<td>M</td>
<td>55</td>
<td>20 years</td>
<td>Prednisolone, hydroxychloroquine</td>
<td>Peripheral blood stem cells transplantation</td>
<td>Remission</td>
</tr>
</tbody>
</table>

**Fig. 1. SIR estimates for HL in SLE.**
In this pattern, the first wave occurs in young adulthood (age 15–35 years), and the second in those over 50 years old. This bimodality could also be seen in the case-reports that we reviewed.

In the general population, overall, HL is more common in males. This phenomena was reflected also in the SLE sample from our multi-centre international cohort study, where 40% of the HL cases were male, although the lupus subjects were predominantly (90%) females; this trend was also suggested for the subjects in our case report review.

Based on our multi-centre cohort study data, the SLE subjects who developed HL appeared to have a survival similar to HL cases in the general population, where the 5-year survival rate is 85% [18, 19]. We cannot comment on the relatively high number of deaths in the case-reports that we reviewed, but this suggests that the case reports may not be unselected, representing mostly severe cases or those with a poor outcome.

Female sex is associated with better survival for Hodgkin’s disease in the general population, as is younger age at time of cancer diagnosis [20, 21]. We have underway a review of the pathology and clinical factors (including stage and other prognostic factors at presentation, treatment, response and relapse) of the lymphoma cases that arose in our SLE sample.

In terms of race as a potential demographic factor of interest, data from the National Cancer Institute suggest that within the regions we studied, the incidence of HL among different racial groups (i.e. white/Caucasians, blacks/African Americans and Hispanics) are similar [19]. That is, incidence estimates for women are in the range of 1–2 cases per 1000 across all of these racial/ethnic groups; for men, incidence estimates are in the range of 2–3 cases per 1000 individuals across all of these racial/ethnic groups. Given this, we believe that the demonstrated increased risk of HL in our subjects does not primarily reflect differences in racial make-up in our SLE sample vs the general population.

One of the characteristic features of Hodgkin’s disease is the presence of anomalous large mono- or multi-nucleated Hodgkin Reed-Steinberg cells [23]. Hodgkin Reed-Steinberg cells are believed to originate from B lymphocytes, specifically from germinal centre (GC) B-cells that have already experienced contact with antigen [24]. Our data regarding the histology of the NHL cases which develop in SLE suggests that these lesions also are derived from a lymphocyte that has already been exposed to antigen [25]. Lymphoma development during the post-antigen exposure stages of differentiation might suggest a role of antigenic stimulation in autoimmune-related lymphomas.

To summarize, the data suggest that risk in SLE is increased not just for NHL but also for other haematological malignancies arising from B-lymphocytes, including HL. Ongoing study of the link between lymphoma and autoimmune diseases such as SLE should focus on clinical and prognostic factors, exposures and outcomes, so that we can further our understanding of the link between autoimmunity and malignancy.

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The authors have declared no conflicts of interest.

References