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Non-Lymphoma Hematological Malignancies in Systemic Lupus Erythematosus

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Abstract

Objective—To describe non-lymphoma hematological malignancies in SLE.

Methods—A large SLE cohort was linked to cancer registries. We examined the types of non-lymphoma hematological cancers.

Results—In 16, 409 patients, 115 hematological cancers (including myelodysplastic syndrome) occurred. Among these, 33 were non-lymphoma. Of the 33 non-lymphoma cases, 13 were of lymphoid lineage: multiple myeloma (N=5), plasmacytoma (N=3), B-cell chronic lymphocytic leukemia, B-CLL (N=3), precursor cell lymphoblastic leukemia (N=1), and unspecified lymphoid leukemia (N=1). The remaining 20 cases were of myeloid lineage: myelodysplastic syndrome, MDS (N=7), acute myeloid leukemia, AML (N=7), chronic myeloid leukemia, CML (N=2), and 4 unspecified leukemias. Most of these malignancies occurred in female Caucasians, except for plasma cell neoplasms (4/5 multiple myeloma and 1/3 plasmacytoma cases occurred in blacks).

Conclusions—In this large SLE cohort, the most common non-lymphoma hematological malignancies were myeloid types (MDS and AML). This contrasts to the general population, where lymphoid types are 1.7 times more common than myeloid non-lymphoma hematological malignancies. Most (80%) multiple myeloma cases occurred in blacks, which requires further investigation.

Keywords

Systemic lupus erythematosus; malignancy; cancer

Introduction

Cancer risk in SLE is a topic of increasing interest, but to date much of the focus has been directed at lymphoma, especially Non-Hodgkin's lymphoma. Our purpose was to describe demographic factors and types of non-lymphoma hematological malignancies in a very large international, multi-site SLE cohort.

Methods

Our assessment was based on a very large international, multi-site cohort drawn from 30 centres, each linked to regional tumour registries to ascertain malignancies. Recently, we have published on the over-all cancer experience in this cohort [1]. In this paper, we describe the types of non-lymphoma hematological cancers occurring after SLE diagnosis, and examine the distribution of demographic characteristics, including sex, race/ethnicity, age, and SLE duration at the time of cancer diagnosis. The centres from which these non-lymphoma hematological cancers in SLE occurred included Canada (Montreal, Toronto, Winnipeg), USA (Chicago, Baltimore, Pittsburgh, Brooklyn, San Francisco, Los Angeles, Chapel Hill, Birmingham), Korea (Seoul), Denmark (Copenhagen), and Sweden (Lund).

The cohort was followed from the date of cohort entry (date first seen in the clinic with confirmed SLE) up to the earliest of: date of last seen in the clinic, death, or end of cancer registry information. Cancer registries generally require at least one calendar year period to have elapsed before they can confirm that their cancer data are adequately complete and accurate, so the end of the observation interval for each centre's SLE cohort was based on the earliest of that date, or the last date the patient was seen in clinic (or date of death, if relevant).

Regional general population cancer rates were obtained and used to generate expected number of hematological malignancies. The total cancers observed in our cohort, divided by

this expected number, provides the standardized incidence ratio (SIR), representing the relative risk of hematologic malignancy in SLE, compared to an age and sex-matched general population.

Results

16, 409 patients were observed for an average of 7.4 person-years. Of these, 90% were female and the majority were Caucasian [1]. In these patients, 115 hematological cancers occurred, and based on age-matched general population cancer rates, the standardized incidence ratio, SIR, for all hematological cancers after SLE onset was 2.9 in females (95% confidence interval, CI 2.3, 3.6) and 3.6 in males (95% CI 2.2, 5.5). The SIR for hematological cancers for SLE patients aged less than 40 was 4.1 (95% CI 2.5, 6.3); in comparison with SLE patients over the age of 60, where the point estimate was SIR 2.3 (95% CI 1.7, 3.1) [1].

We assessed a total of 33 were non-lymphoma hematological malignancies (including myelodysplastic syndrome) that had occurred in these patients. For some context, Figure 1 provides an outline of the cells from which hematological malignancies arise.

For these 33 non-lymphoma hematological cancers, the mean age at cancer diagnosis was 54.3 years (standard deviation, SD, 15.2, median 55), and the mean SLE duration at the time of cancer diagnosis was 14 years (SD 8.2, median 14). Most (30 of the 33) patients were female (90.91%), reflecting the female predominance of the SLE cohort. With respect to race/ethnicity, 18 patients were Caucasian (54.6%), 12 black (of African or Caribbean descent, 36.4%), 2 Asian (6%), and 1 First Nations (Canadian Native).

Of these 33 non-lymphoma cases, 13 were of lymphoid lineage. This included multiple myeloma (N=5), plasmacytomas (N=3), B-cell chronic lymphocytic leukemia, B-CLL (N=3), precursor cell lymphoblastic leukemia (N=1) and lymphoid leukemia not otherwise specified (N=1). The remaining 20 cases were of myeloid lineage. These included myelodysplastic syndrome, MDS (N=7), acute myeloid leukemia, AML (N=7), chronic myeloid leukemia, CML (N=2), and 4 leukemias not otherwise specified.

All of the non-lymphoma lymphoid hematological malignancies in SLE occurred in female Caucasians, except in the plasma cell neoplasms, where 4/5 multiple myeloma cases, and 2/3 plasmacytoma cases were black (the others being Asian and Caucasian, respectively). Regarding age, in B-cell chronic lymphocytic leukemia, the median age of SLE subjects at the time of onset of this cancer was 65 years (range 58 to 83). The median age at onset for this cancer in the female general population is 74 years [2]. At the time of multiple myeloma diagnosis in SLE, median age was 49 years (range 45 to 57), while for the 3 plasmacytoma SLE cases, median age was 35 years (range 25 to 62). In the female general population, the median age at time of diagnosis for multiple myeloma is 70 years [2], and 55 years for plasmacytomas [3].

Of 20 myeloid malignancies, three (15%) occurred in males, and seven of the 20 myeloid malignancies (35%) occurred in blacks. In female AML cases, the median age at AML diagnosis was 48 years (range 34 – 72), versus 66 years in the female general population. The seven MDS cases (6 females) occurred at a median age of 48 years (range 36 – 59), versus 76 years in the general population [2]. The ages at time of diagnosis for the two CML cases (1 female) were similar to the general population median (65 years).

Discussion

Most of the hematological malignancies that developed in our SLE cohort were female, which reflected the fact that 90% of SLE patient are female. In the general population, the risk of hematological cancers is significantly greater in males than females; for example, males have almost twice the risk for B-cell chronic lymphocytic leukemia. Our international cohort study included over 16,000 individuals, and 10% of them were male. Given this, only 2–3 lymphoid malignancies would have been expected in our male SLE subjects. Thus while it may seem unusual that none of the non-lymphoma lymphoid malignancies were male, this may have just been a chance finding due to the low number of males with SLE, and the relative rarity of these cancers in general. Though our SIR point estimate for hematologic cancers in males with SLE (SIR 3.6) was slightly higher than the SIR for females with SLE (SIR 2.9), the confidence intervals did overlap.

Five cases of multiple myeloma occurred in our SLE cohort. Although previous studies were unable to demonstrate that SLE patients have any increased risk for multiple myeloma [4, 5], one large study did demonstrate that patients with a family history of SLE do have an increased risk of developing multiple myeloma [4]. Furthermore, there is also an increased occurrence of SLE in first-degree relatives of people with multiple myeloma [6].We were somewhat surprised that most (80%) of these 5 multiple myeloma cases in our SLE cohort occurred in blacks. In the general population, black populations do have a two-fold increase in multiple myeloma prevalence when compared to Caucasian populations [2]. However, blacks were a minority in our cohort. In our recent review of case reports and case series in the literature, out of 20 SLE patients that developed multiple myeloma [7–24], only one patient was black [22]. Thus, we are unable to explain why such a high proportion of multiple myeloma cases in our cohort, were black.

A striking finding in our study was the young age at diagnoses for the majority of the neoplasms. Of course, given the relatively few number of cases, the results should be interpreted with caution. Still, wth the exception of CML, median onset age for patients in this cohort was 10–20 years earlier than the general population median. While this in part reflects the young age of our cohort, it further emphasizes the increased risk of hematological malignancies in this population. The SIR for hematological cancers according to age suggests that indeed the youngest SLE patients have the highest relative risk, compared to age and sex-matched general population rates.

The most common non-lymphoma hematological malignancies observed in our SLE cohort were myeloid types (MDS and AML). This is in contrast to the general population, where lymphoid types are 1.7 times more common than myeloid types, when lymphomas are excluded [2]. Our observation is similar to previous studies on myeloid malignancies and autoimmune conditions in the literature. A population-based case-control study of hematopoietic malignancies using SEER-Medicare data of 13, 486 myeloid malignancy patients and 160, 086 populationbased controls found that SLE patients had an increased risk of both AML (OR of 1.92) and MDS (OR 1.82) [25]. Another article using a nested case-control study using Swedish registers as well as published case reports of SLE and AML concluded that not only do SLE patients have an increased risk of developing myeloid leukemia, but that this risk is actually restricted to a subset of SLE patients with hematological aberrations such as prolonged leukopenia (OR 14), and to a lesser extent, thrombocytopenia (OR 3.3) [26]. Furthermore, this study demonstrated that 30.4% of their AML cases were preceded by MDS – a rate comparable to the general population [27].

A limitation of our study is that most of our participating centres did not provide information on clinical features, such as disease activity or drugs. We were therefore unable to look at

these variables in the cases. Moreover, with only 9 myeloid leukemia cases (7 AML, 2 CML), we would have difficulty confirming any previously reported association of this malignancy with cytopenias.

Conclusion

In summary, we described the demographics of those who developed hematological malignancies, in our international cohort of 16, 409 SLE patients. Myeloid malignancies such as MDS and AML were the most common; a finding which has been reported before but has not to date received much attention. Most of our non-lymphoma hematological malignancy cases were younger than general population median age-of-onset, although this could simply reflect our cohort demographics. We were surprised by the very high predominance of black race/ethnicity among the SLE patients who developed multiple myeloma. This requires further investigation.

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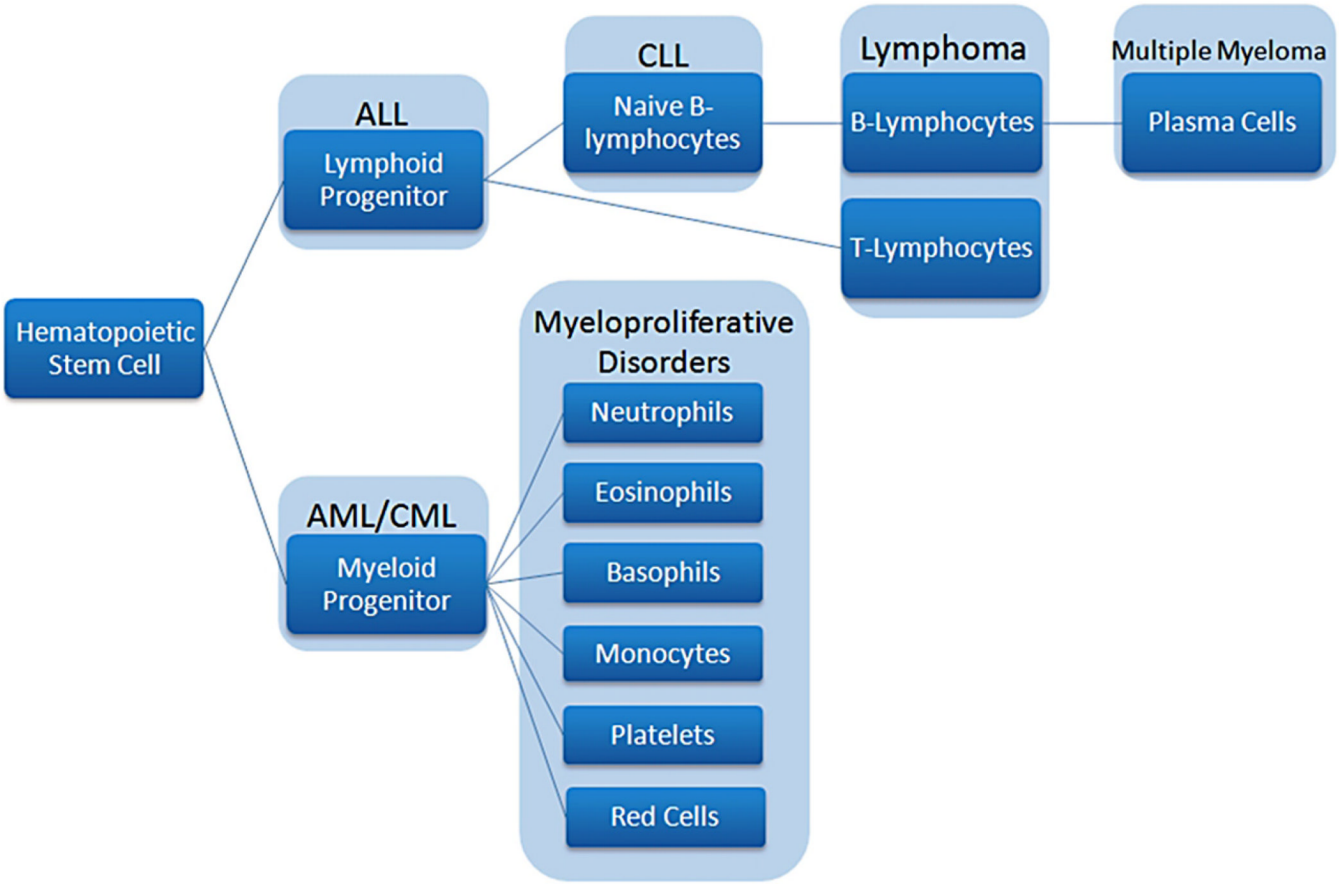

Figure 1.
Hematological Malignancies by Cell Lineage. ALL, acute lymphocytic leukemia; CLL, chronic lymphocytic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia.

Table 1

Demographics of the SLE patients who developed lymphoid malignancies*

Description (ICD-O-3 code)	N	N (White (%)	Median Age at Cancer Diagnosis (Range)	Median SLE duration at Cancer Diagnosis (Range)
Mature B-cell Neoplasms				
B-cell chronic lymphocytic leukemia (9823)	3	3 (100)	65 (58, 83)	11 (8, 23)
Plasma cell Neoplasms				
Multiple Myeloma (9732)	5	1 (20)	49 (45, 57)	17 (8, 25)
Plasmacytoma, NOS (9731)	3	1 (33.3)	35 (25, 62)	14 (11, 25)
Other lymphoid malignancies				
Precursor cell lymphoblastic leukemia, NOS (9835)	1	0	22	0
Lymphoid Leukemia NOS (9820)	1	1 (100)	84	29

Abbreviations: NOS, not otherwise specified.

* All SLE patients who developed lymphoid malignancies were female

** Lymphoblastic leukemias in the general population tend to occur in children, while lymphocytic leukemias tend to occur in older adults.

Table 2

Demographic characteristics of the SLE patients who developed myeloid malignancies

Description (ICD-O-3 code)	No. of Cases	N (%) White	N (%) Female	Median* Age (range)	Median* SLE duration (range)
Acute Myeloid Leukemia	7	5 (71.4)	6 (85.7)	48 (34, 72)	16(5, 23)
AML, NOS (9861)	4	3 (75)	3 (75)	54 (41, 72)	17.5 (16, 21)
Acute monocytic leukemia (9891)	1	0	1 (100)	48	23
Acute myelomonocytic (9867)	1	1 (100)	1 (100)	34	5
AML, multilineage dysplasia (9895)	1	1 (100)	1 (100)	66	10
Myeloproliferative Neoplasms					
CML, NOS (9863)	2	2 (100)	1 (50)	64.5 (62, 67)	14.5 (3, 26)
Myelodysplastic syndrome					
Myelodysplastic syndrome, NOS (9989)	7	2 (28.6)	6 (85.7)	48 (36, 59)	8 (1, 28)
Unknown myeloid neoplasm					
Leukemia, NOS (9800)	2	1 (50)	2 (100)	57.5 (44, 71)	13 (9, 17)
Acute leukemia, NOS (9801)	1	1 (100)	1 (100)	72	5
Myeloid leukemia, NOS (9860)	1	1 (100)	1 (100)	71	12

*At time of cancer diagnosis

Abbreviations: AML, acute myeloid leukemia; CML, chronic myeloid leukemia; NOS, not otherwise specified.