Myeloid leukaemia in systemic lupus erythematosus—a nested case–control study based on Swedish registers

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Objective. To assess the risk factors for leukaemic transformation and myeloid leukaemia in patients with SLE.

Methods. A national SLE cohort identified through SLE discharge diagnoses in the Swedish hospital discharge register during 1964 to 1995 (n = 6438) was linked to the national cancer register. A nested case–control study in SLE patients who developed acute or chronic myeloid leukaemia was performed with SLE patients without malignancy as controls. Medical records from cases and controls were reviewed and bone marrow specimens were re-evaluated. A Medline search of previously published cases of SLE and myeloid leukaemia was performed. Results. After confirmation of SLE diagnosis according to the ACR criteria, eight patients with SLE and myeloid leukaemia and 18 SLE controls were included in the study. Preceding leucopenia was significantly associated with leukaemia development, whereas other SLE manifestations were not. Two cases had a preceding bone marrow confirming myelodysplastic syndrome (MDS). Only two cases were significantly treated with cyclophosphamide or AZA. A Medline search resulted in only 15 previously published cases of coincident SLE and myeloid leukaemia. Preceding MDS was reported in five of these, whereas only eight had been treated with cytotoxic drugs.

Conclusion. Low-dose chemotherapy was not a major cause of myeloid malignancy in our population-based cohort of SLE patients nor in the reported cases from literature. Leucopenia was a risk factor for myeloid leukaemia development and an MDS was frequently seen. Therefore bone marrow investigation should be considered in SLE patients with long-standing leucopenia and anaemia.

Key words: Systemic lupus erythematosus, Acute myeloid leukaemia, Myelodysplastic syndrome, Risk factors, Leucopenia, Cytotoxic drugs.

Introduction

In SLE, an elevated malignancy risk has repeatedly been reported, first and foremost for non-Hodgkin’s lymphoma [1–3]. There are also case reports that suggest an association of SLE with another haematological malignancy, myeloid leukaemia. The first report dates back to 1955 when Lee [4], in an article discussing the clinical value of the LE cell test, describing a male patient with positive LE cell test, who developed myeloblastic leukaemia. Following this, there have been a few case reports and case series of SLE and myeloid leukaemia with a suggested association to usage of cytotoxic drugs [5–6]. However, controlled studies investigating the relationship between acute myeloid leukaemia (AML) and SLE as well as possible risk factors for leukaemia development in SLE patients are lacking.

In a previously published register-based study, we found a doubled risk of leukaemia in a Swedish national SLE cohort [7]. The aim of the current study was to identify risk factors for myeloid leukaemia development in SLE, including exposure to cytotoxic drugs, presence of certain SLE manifestations, cytopenias or a diagnosis of a myelodysplastic syndrome (MDS) by performing a nested case–control study. We also performed a literature search for previously published case reports of SLE with myeloid leukaemia to define clinical phenotypes of SLE and the use of immunosuppressive treatment in these cases.

Patients and methods

Selection of patients and collection of clinical data

From the Swedish Hospital Discharge Register, we identified all patients discharged from hospitals in Sweden with a diagnosis of SLE [International Classification of Diseases (ICD)-7: 456.20; ICD-8: 734.10; ICD-9: 710A] either as a primary or a secondary diagnosis, during 1964–95. We excluded all patients of <20 years of age at the first discharge and those who had ever been discharged with a diagnostic code of RA, PSA or AS. Patients with a discharge diagnosis of cancer before or at the first discharge were also excluded. The study was approved by the local ethics committee at Karolinska Institutet.

On combining the Swedish Hospital Discharge Register with the Swedish Cancer Register, we identified 11 cases of AML (ICD-7 before 1975: 2042, 2046; after 1975: 2050, 206, 2072, 3) and two cases of chronic myelogenous leukaemia (ICD-7 before 1975: 2041; after 1975: 2051) among 6438 patients with SLE. During the greater part of this time period it was not possible to ascertain diagnoses of MDS in the discharge or cancer reports, since the first official MDS classification was implemented only during the late 1980s [8].

To identify risk factors for developing myeloid leukaemia in SLE, a nested case–control study was performed. For each case with SLE and acute or chronic non-lymphocytic leukaemia (n = 13), five controls from the national SLE cohort were randomly selected (n = 65). The controls were matched for gender and were required to have an observation period free from cancer as long as or longer than the matched leukaemia–SLE case.

From the Swedish Hospital Discharge Register, the medical records from the hospital admissions of each patient were identified and requested. We also retrieved medical records from previous or subsequent visits to outpatient clinics. One (8%) case and eight (12%) controls could not be evaluated due to missing medical records. Seventeen (26%) control patients had a diagnosis code of tuberculosis Y34.19 or 734.19, which was misinterpreted by the computer program as the code for SLE (734.10) and were excluded. In total, medical records were retrieved for 52 patients (12 cases and 40 controls) who had been treated in 43 different...
Myeloid leukaemia in SLE

Also included treatment, medical events and co-morbidities.

Drugs, respectively. Data retrieved from the medical records

two or more occasions and <100,000/mm³ in the absence of offending
drugs, respectively. Data retrieved from the medical records

also included treatment, medical events and co-morbidities.

Retrospective bone marrow analysis

From the medical records we identified code numbers of the tissue
specimens on which the leukaemia diagnosis was based. The
original slides were collected from five Swedish pathology
departments and were reviewed by an experienced haematopathologist
(C.S.). The bone marrow specimens in two out of eight cases
included both a haematoxylin-eosin (HE)-stained section of a
bone marrow clot or trephine biopsy and May–Grünwald–
Giemsa-stained smears. In four cases HE sections and in one
only smears were available. In one case, the diagnosis was based
on autopsy material from bone marrow and lymph node
completed with immunostainings for lymphocyte markers and
myeloperoxidase. Specimens were examined in a light microscope
equipped with a 60× oil immersion lens. Sections of bone marrow
allowed evaluation of cellularity and smears allowed the study of
cell components and differential cell counts. Leukaemias were
classified according to the WHO classification [8]. Due to the
lack of additional material, no complementary enzyme staining
or immunophenotype analysis could be done allowing for a sub-
classification of the leukaemias. The diagnostic process of acute
leukaemia between 1964 and the end of the 1980s did not routinely
include a chromosomal analysis, which is why these data could
not be retrieved in the present cohort, except in one case.

Medline search

To collect previously published cases of coincident SLE and
myeloid leukaemia, we performed a Medline search on the
topics SLE and acute/chronic, myeloid/myelogenous/non-
lymphocytic leukaemia for the time period 1965–2007. Reference
lists from published case reports were checked for possible cases
that might have been missed in the initial search. Case reports
were assessed and like the cases from our study evaluated
with respect to the clinical features of the rheumatic disease and
immunosuppressive treatment. Case reports written in a language
other than English were omitted (n = 2, Polish and Japanese).

Statistics

The statistical methods used were odds ratio (ORs) with 95% CIs.
These were calculated with Statistical Package for the Social
Sciences (SPSS).

Results

SLE diagnosis evaluation

Medical records were available from 12 SLE patients with myeloid
leukaemia. Of these, four were excluded for not fulfilling the ACR
criteria for SLE: two had drug-induced SLE, with remission
from SLE symptoms after drug cessation (SSZ and hydralazine,
respectively), the other two fulfilled only two ACR criteria. The
remaining eight (67%) cases—out of 12—with SLE and myeloid
leukaemia were included in the study, and their clinical haemato-
logical malignancy diagnoses were subject for re-evaluation and
retrospective bone marrow analysis (Table 1).

Forty SLE control non-leukaemia patients were subject to
evaluation of medical records. Eighteen (45%) fulfilled the ACR
criteria for SLE and were included in the study. Of those excluded,
11 patients did not fulfill at least four ACR criteria for SLE and
11 had drug-related lupus (eight hydralazine; two procainamide;
and one quinidine).

Evaluation of leukaemia diagnosis

In seven cases, re-evaluation of bone marrow specimens confirmed
the original leukaemia diagnosis. In the remaining case (n=4) two
bone marrow biopsies were performed during a phase with moder-
ate to severe pancytopenia—one with a dry tap result and one
showing a bone marrow disorder not really compatible with leu-
kaemia. A month later, a marked leukocytosis with >50% blast

Table 1. Cases of SLE and myeloid leukaemia

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age at SLE diagnosis, years</th>
<th>SLE features</th>
<th>SLE treatment with AZA/CTX: time, months; estimated total dose, g</th>
<th>Haematological events between SLE and leukaemia diagnosis, months from SLE diagnosis</th>
<th>Clinical diagnosis of leukaemia, haematological event, months from SLE diagnosis</th>
<th>Survival time from AML/CML, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>56.5</td>
<td>Photosens, arthritis, pleuritis, leucop., thyro., IgM*, DNA and ANA</td>
<td>No</td>
<td>WBC&lt;, Plt&lt;, 12 Hb&lt;, 29</td>
<td>AML, 30</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>63.5</td>
<td>Pleuropericarditis, pleuritis, IgG* and ANA*</td>
<td>AZA; 2</td>
<td>WBC&lt;, 21*</td>
<td>Chronic myeloid monocytic leukaemia, Hb, Plt&lt;, 29</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>69</td>
<td>Erythema, arthritis, pleuritis, thyro., leucop., IgG* and ANA</td>
<td>No</td>
<td>WBC&lt;, 5</td>
<td>Acute myeloblastic leukaemia, 9</td>
<td>&lt;2</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>29</td>
<td>Malar rash, SCLE, photosens, arthritis, leucop., thyro., IgG* and ANA</td>
<td>AZA; 6 + 6; 55</td>
<td>WBC&lt;, 12*</td>
<td>Acute myeloblast leukaemia, Hb&lt;, Plt&lt;, 1 71</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>52</td>
<td>Cutaneous LE, arthritis, pleuritis, leucop., IgG* and ANA* and LE cells</td>
<td>No</td>
<td>WBC&lt;, 102</td>
<td>AML, 1, WBC&lt;, Hb&lt;, Plt&lt;, 1 38</td>
<td>&lt;2</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>77</td>
<td>Arthritis, pleuritis, DNA and ANA*</td>
<td>No</td>
<td>Hb&lt;, 44</td>
<td>AML, Plt&lt;, WBC&lt;, 47</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>50.5</td>
<td>Pleuritis, glomerulonephritis, thyro., leucop. and ANA</td>
<td>AZA; 18; 50 CTX; 48; 120</td>
<td>Plt&lt;, WBC&lt;, Hb&lt;, 30</td>
<td>AML M5b, Hb&lt;, 1 100</td>
<td>18</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>60</td>
<td>Arthritis, pleuritis, DNA and ANA*</td>
<td>No</td>
<td>WBC&lt;, 120</td>
<td>Chronic myelogenous leukaemia, 1 92</td>
<td>6</td>
</tr>
</tbody>
</table>

*Bone marrow biopsy and smear taken (without signs of leukaemia).
*Normalized after AZA withdrawal. M: male; F: female; DNA: antibodies to native DNA; LE cells: positive LE cell phenomenon;
IgG, IgM: elevated immunoglobulins; thyro.: thyrocytopenia; leucop.: leucopenia; photosens.: photosensitivity; Hb: haemoglobin; WBC: white blood cell count; Plt: platelet count; CTX: cyclophosphamide.
cells was found in peripheral blood and a diagnosis of acute myeloblastic leukaemia was made.

**Phenotypes and leukaemia risk factors**

A minority of the eight cases with leukaemia and SLE were males (Table 2). Among the cases, age at onset of the SLE disease showed great variation, with a median of 60 (range 29–77) years compared with 59.5 (range 18–74) years for the SLE controls. The period between SLE and leukaemia diagnosis varied between 1 and 17 years with a median of 5 years. The median survival time after leukaemia diagnosis was 6.5 (range 1–18) months.

Haematological abnormalities were more common among the SLE–leukaemia cases. For leucopenia, the difference reached statistical significance (OR 14; 95% CI 1.4, 41) (Table 2).

During the disease course, all eight cases who developed leukaemia had laboratory abnormalities in one, two or three of the haematological cell lines prior to diagnosis. A bone marrow biopsy prior to leukaemia diagnosis was made in four of the eight cases (Table 1). In two of these, there were dysplastic changes indicative of MDS. In two cases (Cases 4 and 7), there was a possible association between anaemia, leuco- or thrombocytopenia and treatment with AZA or cyclophosphamide, but the exposure to cytotoxic drugs did not differ between the SLE cases and the SLE controls. The presence of serious organ manifestations such as CNS involvement or glomerulonephritis was not significantly different between the SLE cases and the SLE controls (Table 2).

**SLE–myeloid leukaemia cases in literature**

We found 14 case reports of SLE and AML (one of these was Case 3 in our study) and one with SLE and chronic myelogenous leukaemia (the 14 non-Swedish cases are presented in Table 3) through a literature search.

Median age at SLE diagnosis among these was considerably lower than among our study cases, 41 years compared with 60 years. On the other hand, the median duration between SLE and leukaemia diagnosis was not different between the published cases and our cohort—4 vs 5 years. In six of the reported cases, there was information on a bone marrow investigation before the leukaemia diagnosis. In five cases, signs of myelodysplastic features in the biopsy were mentioned. Four of the 14 non-Swedish cases were men. Eight (53%) cases had been treated with cytotoxic drugs for their rheumatic disease prior to the leukaemia diagnosis, seven with AZA and four with cyclophosphamide (Table 3). Leukaemia outcome was just as poor as in our cases in 11 out of 15 reported cases with death within a few months, but four cases—all in the 1990s or later—had a longer survival.

**Discussion**

The presence of haematological abnormalities, anaemia, leucopenia and to a lesser extent thrombocytopenia are common clinical manifestations of the SLE disease, often independent of disease severity. Most SLE patients are subject to regular check-ups for clinical manifestations and by laboratory tests, making it possible to determine if a gradual transition had occurred in our cases from cytopenias via MDS to AML. Interestingly, leucopenia was the only clinical SLE-associated finding with a significantly elevated OR for leukaemia development. As stated in Results section, both among our cases and those from the literature, concern of cytopenias had often been raised and a bone marrow biopsy had been performed—before the time point when the leukaemia diagnosis was made. In several of these bone marrow biopsies findings compatible with MDS were seen. The frequency of a preceding myelodysplastic phase before leukaemia was at least comparable with the estimated 25% that has been observed in the general leukaemia population [24].

Some previously known associations between rheumatic diseases and leukaemia do exist. In a population-based cohort of Wegener’s granulomatosis, a more than 5-fold increased risk of leukaemia was found [25]. A subsequent nested case-control study on urinary bladder cancer in the same cohort showed, not unexpectedly, that ~90% of the patients had been treated with often high cumulative doses of CTX [26]. Furthermore, AS patients, who during the 1950s were exposed to radiation treatment with X-ray or multiple injections of 224Ra, demonstrated a high risk of myeloid leukaemia and this was thought to be related to these exposures [27, 28].

Although, among our cohort of SLE patients, the possibility of a therapy-related AML could not be ruled out in two patients, Cases 4 (AZA) and 7 (CTX), low-dose chemotherapy was not associated with myeloid malignancy nor in the reported cases from the literature. However, alkylating drugs, like many other

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**Table 2. Gender, medical treatment and clinical characteristics in SLE cases with myeloid leukaemia and SLE controls**

<table>
<thead>
<tr>
<th></th>
<th>SLE patients with leukaemia, n=8</th>
<th>SLE patients–controls, n=18</th>
<th>OR (95% CI)</th>
<th>Literature cases, n=15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, female</td>
<td>3 (38)</td>
<td>9 (50)</td>
<td>1.2 (0.08, 1.5)</td>
<td>10 (67)</td>
</tr>
<tr>
<td>Oral glucocorticoids</td>
<td>8 (100)</td>
<td>15 (83)</td>
<td>0.5 (1.3, 3)</td>
<td>13 (87)</td>
</tr>
<tr>
<td>Anti-malarials</td>
<td>2 (25)</td>
<td>7 (39)</td>
<td>0.5 (0.1, 2.1)</td>
<td>8 (53)</td>
</tr>
<tr>
<td>Cytotoxic agents</td>
<td>3 (38)</td>
<td>11 (55)</td>
<td>0.8 (0.1, 4.1)</td>
<td>7 (47)</td>
</tr>
<tr>
<td>Aza</td>
<td>3 (38)</td>
<td>8 (44)</td>
<td>0.4 (0.1, 3.8)</td>
<td>4 (27)</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>1 (12)</td>
<td>5 (28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malar rash</td>
<td>1 (12)</td>
<td>2 (11)</td>
<td>1.1 (0.1, 14.8)</td>
<td>5 (38)</td>
</tr>
<tr>
<td>Diacloid rash</td>
<td>2 (25)</td>
<td>5 (28)</td>
<td>0.9 (0.1, 5.8)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>2 (25)</td>
<td>6 (33)</td>
<td>0.7 (0.1, 4.3)</td>
<td>5 (38)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>6 (75)</td>
<td>15 (83)</td>
<td>0.6 (0.1, 4.5)</td>
<td>11 (85)</td>
</tr>
<tr>
<td>Pleuritis</td>
<td>7 (88)</td>
<td>11 (61)</td>
<td>4.4 (0.4, 44.4)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Recurrent pneumonias</td>
<td>2 (25)</td>
<td>3 (17)</td>
<td>1.7 (0.2, 12.6)</td>
<td>3 (23)</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>1 (12)</td>
<td>7 (39)</td>
<td>0.2 (0.1, 2.2)</td>
<td>5 (38)</td>
</tr>
<tr>
<td>Epilepsy, psychosis</td>
<td>1 (12)</td>
<td>4 (22)</td>
<td>0.5 (0.1, 5.3)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>7 (88)</td>
<td>6 (33)</td>
<td>1.4 (1.4, 141)</td>
<td>5 (38)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5 (62)</td>
<td>6 (33)</td>
<td>3.3 (0.6, 18.9)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Autoimmune haemolytic anaemia</td>
<td>0</td>
<td>2 (25)</td>
<td>1.1 (0.1, 14.8)</td>
<td>5 (38)</td>
</tr>
<tr>
<td>ANA</td>
<td>8 (100)</td>
<td>17 (94)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DNA</td>
<td>2 (25)</td>
<td>5 (28)</td>
<td>0.9 (0.1, 5.8)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Elevated IgG</td>
<td>5 (62)</td>
<td>7 (39)</td>
<td>2.6 (0.5, 14.5)</td>
<td>4 (31)</td>
</tr>
<tr>
<td>Coombs test positive</td>
<td>1 (12)</td>
<td>3 (17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complement aberration</td>
<td>1 (12)</td>
<td>4 (22)</td>
<td>0.5 (0.1, 5.4)</td>
<td>6 (46)</td>
</tr>
</tbody>
</table>

Values are given as n (%) unless otherwise mentioned. Literature cases for comparison. aNot the ref. [22]. DNA: antibodies to native DNA.
TABLE 3. Previously published cases of SLE and myeloid leukaemia

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age at SLE diagnosis, years</th>
<th>SLE features</th>
<th>Haematological events from SLE diagnosis to AML diagnosis, months from SLE diagnosis</th>
<th>Clinical diagnosis of leukaemia, haematological event, months from SLE diagnosis</th>
<th>Survival after AML diagnosis, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>[11]</td>
<td>57</td>
<td>Rash, photosens., polyarthritis, pneumonias, leucop. and LE</td>
<td>WBC&lt;sub&gt;a&lt;/sub&gt;, Hb&lt;sub&gt;a&lt;/sub&gt;&lt;sup&gt;+&lt;/sup&gt;, 48</td>
<td>Acute myeloblastic leukaemia, pancytop., 60</td>
<td>&lt;1</td>
</tr>
<tr>
<td>[12]</td>
<td>23</td>
<td>Rash, photosens., polyarthritis, perimyocarditis, CNS vasculitis, ANA and LE</td>
<td>AZA; 10; 52</td>
<td>Acute myelomonocytic leukaemia, Hb&lt;sub&gt;i&lt;/sub&gt;, Plt&lt;sub&gt;i&lt;/sub&gt;, WBC&lt;sub&gt;i&lt;/sub&gt;, 31</td>
<td>2</td>
</tr>
<tr>
<td>[13]</td>
<td>31</td>
<td>Arthritis, nephrotic syndrome (membr. GN), ANA and LE</td>
<td>Hb&lt;sub&gt;i&lt;/sub&gt;, WBC&lt;sub&gt;i&lt;/sub&gt;, 24&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Acute myelomonocytic leukaemia pancytop.&lt;sup&gt;+, 72&lt;/sup&gt;, pancytop.&lt;sup&gt;+, 25&lt;/sup&gt;</td>
<td>2</td>
</tr>
<tr>
<td>[14]</td>
<td>55</td>
<td>Discoid rash, alopecia, nephritis, ANA, DNA and LE</td>
<td>CTX; 12; 4</td>
<td>Erythro leukaemia Hb&lt;sub&gt;i&lt;/sub&gt;, WBC&lt;sub&gt;i&lt;/sub&gt;, 29</td>
<td>A few months</td>
</tr>
<tr>
<td>[15]</td>
<td>69</td>
<td>Same patient as Case 3 in Table 2</td>
<td>WBC&lt;sub&gt;i&lt;/sub&gt;, 5</td>
<td>Acute myeloblastic leukaemia, 9</td>
<td>&lt;2</td>
</tr>
<tr>
<td>[16]</td>
<td>10</td>
<td>Malar rash, photosens., leucop., AIHA, IgG and ANA</td>
<td>AML&lt;sub&gt;i&lt;/sub&gt;, Hb&lt;sub&gt;i&lt;/sub&gt;, WBC&lt;sub&gt;i&lt;/sub&gt;, 10</td>
<td>A few months</td>
<td>9</td>
</tr>
<tr>
<td>[17]</td>
<td>67</td>
<td>Purpura, polyarthritis, thr. cytop. (ITP), leucop. ANA and LE</td>
<td>Hb&lt;sub&gt;i&lt;/sub&gt;&lt;sup&gt;+&lt;/sup&gt;, 18</td>
<td>Acute myelogenous leukaemia, WBC&lt;sub&gt;i&lt;/sub&gt;, 20</td>
<td>A few months</td>
</tr>
<tr>
<td>[18]</td>
<td>24</td>
<td>Polyarthritis, myocardiitis, pneumonitis, lupus cerebritis, ANA and LE</td>
<td>AZA; 9; 40</td>
<td>Acute myelogenous leukaemia, Hb&lt;sub&gt;i&lt;/sub&gt;, Plt&lt;sub&gt;i&lt;/sub&gt;, WBC&lt;sub&gt;i&lt;/sub&gt;, 9</td>
<td>A few months</td>
</tr>
<tr>
<td>[19]</td>
<td>67</td>
<td>Polyarthritis, prolifer., sclerosing GN, leucop. and ANA</td>
<td>CTX; 12; 4</td>
<td>Acute non-lymphocytic leukaemia M2, WBC&lt;sub&gt;i&lt;/sub&gt;, 92</td>
<td>A</td>
</tr>
<tr>
<td>[20]</td>
<td>32</td>
<td>Malar rash, polyarthritis, proteinuria, CNS vasculitis, AIHA and ANA</td>
<td>AZA; 10; 30</td>
<td>Acute myelomonocytic leukaem. w. abn. eosinophils M4 pancytop., 38</td>
<td>A</td>
</tr>
<tr>
<td>[22]</td>
<td>68</td>
<td>Malar rash, photosens., oral ulcers, polyarthritis, IgG1 and ANA</td>
<td>CTX; 2; 1,7</td>
<td>Acute megakaryoblastic leukaemia M7 pancytop., 48</td>
<td>A few months</td>
</tr>
<tr>
<td>[23]</td>
<td>44</td>
<td>Info missing, but diffuse prolif. GN</td>
<td>CTX; 24; 37</td>
<td>AML M2 pancytop., 54</td>
<td>&lt;1</td>
</tr>
<tr>
<td>[24]</td>
<td>41</td>
<td>Urticaria, photosens., arthralgia, pneumonitis, pericarditis and nephritis</td>
<td>WBC&lt;sub&gt;i&lt;/sub&gt;, 25</td>
<td>AML M4 pancytop., 96</td>
<td>C</td>
</tr>
<tr>
<td>[25]</td>
<td>40</td>
<td>Info missing</td>
<td>CTX; 6; 5.4</td>
<td>AML M6, WBC&lt;sub&gt;i&lt;/sub&gt;, 108</td>
<td>D</td>
</tr>
</tbody>
</table>

<sup>a</sup>Bone marrow biopsy and smear taken (without signs of leukaemia). <sup>b</sup>Normalized after AZA withdrawal. Other outcome than survival time: A: BMF follow-up shows mild hypocellularity and normal karyotype. No evidence of lupus activity; B: 2.5 years after autologous bone marrow transplantation in complete haematological remission without clinical and serological evidence of autoimmune disease; C: marrow remission, under evaluation for bone marrow transplantation; D: in remission after allogenic stem cell transplantation. Photosens.: photosensitivity; membr. prolif. GN: membranous proliferative glomerulonephritis; leucop.: leucopenia; thr. cytop.: thrombocytopenia; pancytop.: pancytopenia; AIHA: autoimmune haemolytic anaemia; DNA: antibodies to native DNA; LE-cells: positive LE cell; IgG: elevated immunoglobulin; Hb: haemoglobin; WBC: white blood cell count; Plt: platelet count; CTx.: cyclophosphamide; M: male; F: female; Cau: Caucasian; Chi: Chinese; Jap: Japanese; AmInd: American-Indian; NS: not stated.

Chemotherapeutic drugs, constitute one of the relatively few known aetiological risk factors for leukaemia. Another is ionizing radiation [10]. Our study encompassed cases included up to 1995, when new treatment modalities like mycopHENolate MOFetile for lupus nephritis had not yet been adopted, and CTX was the primary drug in severe SLE cases. Notably, our subset of SLE patients with leukaemia rarely presented with severe organ manifestations like nephritis or CNS manifestations. AZA is an anti-metabolite that has been used in SLE treatment since the 1960s both for treating disease manifestations and as a glucocorticoid-sparing drug. It could induce defective DNA mismatch repair, possibly promoting survival of cells for a leukemic clone but had rarely been used among our SLE cases with leukaemia [29]. On the contrary, anti-malarial drugs, chloroquine and HCQ, are immune modulating drugs often used in patients with SLE that have recently been reported to exert anti-neoplastic properties. They are strongly DNA intercalating, preventing mutations in cells with a high mitotic rate and improving cellular mechanisms of DNA repair after the damage was caused by alkylating therapy [30]. Unfortunately, our study did not have the statistical power to support such a protecting effect from anti-malarials.

The study design—retrospective scrutinizing of hospital charts—has several limitations most obviously that information being relevant for diagnosis according to the ACR criteria may be missing, e.g. mild symptoms such as oral ulcers. Moreover, some laboratory tests like anti-Sm or aPL antibodies may not have been checked for—or were not available during the study period. This design and our selected inclusion criteria—strictly applying the ACR classification criteria—probably excluded some ‘true SLE cases’ and contributed to the large number of cases and controls that were excluded. In addition, using the hospital discharge register to identify SLE cases brought some non-medical causes of exclusions; the administrative imperfections of the ICD discharges and the ACR classification criteria—probably excluded some ‘true SLE cases’ and contributed to the large number of cases and controls that were excluded. In addition, using the hospital discharge register to identify SLE cases brought some non-medical causes of exclusions; the administrative imperfections of the ICD codes, numbers, which misnumbering of tuberculosis and the lack of a separate diagnosis code for drug-induced SLE. However, the exclusions were both among cases and controls and do not affect the estimation of risk factors for myeloid leukaemia. A strength of using the hospital discharge register is that it identifies a large number of cases but cannot be ruled out due to the hospitalization per se, however. Since there was a greater number of excluded cases (the denominator) than cases (the numerator), when the SLE diagnosis of register-identified cases was validated we can assume with some certainty that the increased (doubled) risk of myeloid leukaemia in SLE compared with the general Swedish population observed in a previous register-based study does not represent an overestimation [7]. On the contrary, it is probably an underestimation of the true risk. Interestingly, the risk of myeloid leukaemia seems to be
confined to a certain subgroup of lupus patients. This subgroup is characterized by a gender proportion (more men) and a higher age at onset of SLE not usually seen when describing SLE patient characteristics. We could speculate that these patients constitute a group of ‘survivors’ spared from aggressive inflammatory SLE organ manifestations and with an age when cancer is becoming increasingly more common and where also an MDS can occur.

In conclusion, SLE patients have an increased risk to develop myeloid leukaemia. Our data suggest that only a minority of the leukaemias that arise in SLE might be therapy related. We acknowledge inherent limitations in our methods. Still, based on the data, we believe that leukaemia risk should not be a reason to avoid immunosuppressive treatment in the face of serious SLE manifestations. Our data and previously published cases rather suggest that the leukaemia risk may be confined to a subset of SLE patients with predominating haematological aberrations. Cytopenia in SLE patients caused by bone marrow suppressive agents is not possible to distinguish from cytopenia resulting from an early MDS by analysis of the peripheral blood only. SLE patients with prolonged cytopenias and in particular leukopenia should therefore, irrespective of treatment, be subject to a bone marrow investigation.

### References


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### Rheumatology key messages

- Leukaemia risk may be confined to a subset of SLE patients with predominating haematological aberrations.
- Persistent leucopenia and anaemia in SLE patients should raise awareness.