Abstract. Background: With the development of modern therapies and better care of patients with autoimmune rheumatic diseases (ARDs) increased survival has been achieved. However, ARDs may share an association with risk of lymphomas and solid tumors. The increased cancer risk in these patients is mainly due to high inflammatory activity and severity of disease, rather than the immunosuppressive therapy. Patients and Methods: We studied the coexistence or later development of cancer with ARDs in a retrospective audit of a reference university hospital and critically reviewed published literature. Fourteen out of 1,730 patients with rheumatoid arthritis (RA) and Sjogren’s syndrome (SS) followed-up at the University Hospital of Ioannina over the last 33 years developed secondary malignancies, both solid tumors and lymphomas. Results and Conclusion: The most frequent cancer associated with ARDs is diffuse large B-cell lymphoma (DLBCL). The average risk of lymphoma in RA may be composed of a markedly increased risk in patients with most severe disease. Solid tumors were presented mainly in RA patients and renal cell carcinoma was the most frequently found.

The dual relationship between autoimmunity and cancer has long been recognized. It has been shown that there is an increased risk of malignancies, mainly non-Hodgkin lymphoma (NHL), in patients with rheumatoid arthritis (RA), Sjogren’s syndrome (SS), and systemic lupus erythematosus (SLE) (1-8). In initial studies (7, 8), the more indolent mucosa-associated lymphoid tissue (MALT) lymphoma was the most common lymphoma seen in primary SS. Mechanisms that possibly contribute to the increased incidence of lymphoma in autoimmune rheumatic diseases (ARDs) include immune dysregulation, resistance to apoptosis and prolonged survival of B cells, chronic antigenic stimulation and challenged T-cell function. At the molecular level, the transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells (NF-ĸB) appears to be a key connecting element between inflammation and cancer (16). NF-ĸB is a central intracellular transducer of inflammatory signals integrating signals from a variety of environmental changes, including infection, tissue damage and autoimmunity (16, 17).

The role of immunosuppressive medications in the development of cancer and/or lymphoma in SLE is still controversial. Non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticosteroids do not appear to be associated with increased risk of malignancy in patients with RA or other ARDs (1, 18). The overall malignancy risk attributable to methotrexate treatment in patients with ARDs does not appear to be increased, although there are numerous reports suggesting that the risk of lymphoproliferative diseases may be increased. When patients are on long-term immunosuppressive medications, the odds of cancer development are increased (19, 20). It has also not been shown an increased risk of malignancies associated with anti-TNF (tumor necrosis factor) treatment for RA (21). In some cases, common environmental risk factors for chronic inflammatory diseases and malignancy contribute to increased comorbidity (22). In the present article, we are presenting our experience on this association by describing 14 cases from our cohort with ARDs who developed hematological and non-hematological malignancies.

Materials and Methods

The records of patients with ARDs diagnosed and treated at the Rheumatology Department of Ioannina University Hospital, Greece, were investigated from 1981 to 2013 for the development of malignant diseases. Patients diagnosed with SS and RA were included in this study. Types of cancer, anticancer treatment and
survival were analyzed. Also, the elapsed time from the diagnosis of ARDs to cancer development as well as the administration of various anti-rheumatic treatments was recorded.

Results

Cancer detection. Fourteen patients with cancer were retrieved in total among 1,730 patients with RA and SS from the database of the University hospital of Ioannina, Greece, between 1981 and 2013 (Table I). Ten cases with cancer were identified out of 1,280 patients with RA, (incidence of 0.8%), and 5 out of the 450 patients with SS, (incidence of 1.1%). One patient had secondary SS with RA.

Autoimmune parameters. RA accounted for the majority of the patients (10/15) and almost all of them presented with moderate or severe disease. We identified these 10 cases diagnosed with a secondary malignancy out of 1,280 patients with RA that were registered in the Rheumatology division from 1981 (0.8%), and 5 out of the 450 patients with SS, (incidence of 1.1%). One patient had secondary SS with RA.

Cancer parameters. The mean age of the autoimmune patients at the time of the diagnosis of cancer was 62.6 years (range=52-72 years) with a strong female predisposition (8 out of 15 patients). Seven patients diagnosed with ARDs developed lymphomas. Five of them presented with diffuse large B-cell lymphoma (DLBCL) of stage IV in three cases and stage II in the rest two patients. The remaining two patients were diagnosed with extranodal marginal zone lymphoma of stage IV and nodular sclerosis Hodgkin’s lymphoma of stage IIIb, respectively. All patients were treated with chemotherapy, 5 of whom enjoyed long term survival.

Eight ARDs patients developed solid tumors. Seven of them had RA and were diagnosed with renal cell carcinomas of stage I and of grade III in three cases and the rest with hepatocellular, colon, breast carcinomas, as well as pulmonary carcinoid tumor. Only two patients with solid tumors (hepatocellular carcinoma and colon cancer) presented with metastatic disease. The remaining cases had early-stage disease. As far as systemic treatment is concerned, four out of eight patients received chemotherapy, endocrine or targeting therapy and some of them experienced long-term survival.

Discussion

The direct link between autoimmunity and lymphoma development has been supported by large epidemiological studies showing a consistent risk increase of lymphoma associated with certain autoimmunity and inflammatory conditions in independent cohorts from different countries. It is apparent that the magnitude of the risk estimates varies

Table I. Cancer diagnosis in patients with ARDs: Demographics.

<table>
<thead>
<tr>
<th>Case</th>
<th>Cancer histology</th>
<th>Preexisting ARD</th>
<th>Gender</th>
<th>Age at diagnosis</th>
<th>ARD severity</th>
<th>Tumor stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>L.A.</td>
<td>DLBCL</td>
<td>RA, SS</td>
<td>Female</td>
<td>27</td>
<td>57</td>
<td>Severe</td>
</tr>
<tr>
<td>F.E.</td>
<td>DLBCL</td>
<td>RA</td>
<td>Male</td>
<td>40</td>
<td>62</td>
<td>Severe</td>
</tr>
<tr>
<td>R.A.</td>
<td>DLBCL</td>
<td>RA</td>
<td>Male</td>
<td>49</td>
<td>58</td>
<td>N/A</td>
</tr>
<tr>
<td>S.C.</td>
<td>DLBCL</td>
<td>SS</td>
<td>Male</td>
<td>42</td>
<td>68</td>
<td>Moderate</td>
</tr>
<tr>
<td>S.G.</td>
<td>DLBCL</td>
<td>SS</td>
<td>Female</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>S.R.</td>
<td>Nodular sclerosis Hodgkin’s lymphoma</td>
<td>SS, Male</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>T.T.</td>
<td>Extranodal marginal zone lymphoma</td>
<td>SS, Male</td>
<td>47</td>
<td>67</td>
<td>Moderate</td>
<td>Stage IV</td>
</tr>
<tr>
<td>A.A.</td>
<td>Ductal carcinoma in situ of the breast</td>
<td>RA, Female</td>
<td>50</td>
<td>62</td>
<td>Moderate</td>
<td>Stage 0, grade II</td>
</tr>
<tr>
<td>T.A.</td>
<td>Lung carcinoid tumor</td>
<td>RA, Female</td>
<td>54</td>
<td>70</td>
<td>Moderate</td>
<td>T1bN0M0, stage I</td>
</tr>
<tr>
<td>F.K.</td>
<td>Hepatocellular Carcinoma</td>
<td>RA, Female</td>
<td>46</td>
<td>65</td>
<td>Moderate</td>
<td>Stage IV</td>
</tr>
<tr>
<td>V.F.</td>
<td>Colon carcinoma</td>
<td>RA</td>
<td>Male</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>P.M.</td>
<td>Clear cell renal cell carcinoma</td>
<td>RA, Female</td>
<td>22</td>
<td>52</td>
<td>Moderate</td>
<td>T1bN0M0, stage I, grade III</td>
</tr>
<tr>
<td>H.A.</td>
<td>Clear cell renal cell carcinoma</td>
<td>RA, Female</td>
<td>55</td>
<td>56</td>
<td>Moderate</td>
<td>T1aN0M0, stage I, grade III</td>
</tr>
<tr>
<td>B.E.</td>
<td>Clear cell renal cell carcinoma</td>
<td>RA, Female</td>
<td>45</td>
<td>72</td>
<td>Moderate</td>
<td>T1aN0M0, stage I, grade III</td>
</tr>
</tbody>
</table>

ARDs, Autoimmune rheumatic diseases; DLBCL, diffuse large B-cell lymphoma; SS, Sjogren’s syndrome; RA, rheumatoid arthritis; N/A, not available.
considerably between studies. Earlier and smaller studies on selected patients typically reported higher risk estimates compared to more recent, larger and population-based studies (23-25). The highest relative risk (RR) for lymphoma is associated with primary Sjogren’s syndrome (pSS), followed by SLE and RA, indicating a disease-specific risk profile (26). Data from all available population-based register studies with estimates of lymphoma, breast, lung and colorectal cancer in patients with ARDs are depicted in Table III.

The most frightening complication of pSS is lymphoproliferative disease. This is a chronic excessive salivary and lacrimal gland B cell stimulation and impaired B cell apoptosis that leads to tumorigenesis and clonal expansion of B cells. In large cohorts, the estimated odds ratio of lymphoma in SS was between 2.0 and 18.8 (27, 28). A recent population-based case-control study found that marginal zone lymphoma was most strongly associated with SS, followed by DLBCL and that these associations remained significant when the 5-year period prior to diagnosis was excluded (29). In contrast, several clinical analyses indicated that MALT and DLBCL lymphomas occurred at a similar frequency (30). It is also observed that the RR of developing lymphoma was about 16-fold higher in SS patients than in the general population and that this risk is increased over time and remained high, even 15 years after pSS diagnosis (30). The overall 10-year survival rates were estimated to be 91% for patients with SS and 69% for patients who developed lymphoma (31). Moreover, some
studies have reported that pSS patients who developed lymphoma were at higher risk of developing a second malignancy, probably due to suppressed immunity (32). The salivary glands are the most common site of lymphoma development but extra-nodal sites are also involved, including the stomach, nasopharynx, skin, liver, kidneys, lungs, lymph nodes and bone marrow (33). SS may occur alone (primary SS) or in association with another ARD, defined as secondary SS. Secondary SS can be associated with SLE. The Inter Lymph consortium of non-Hodgkin’s lymphoma (NHL) case-control studies found that patients with secondary SS were at higher risk of NHL development than patients with pSS, with similar RR for NHL subtypes (8). Nevertheless, we did not find any relationship between infectious agents and lymphoma development in our series.

The risk of cancer has been extensively studied in patients with RA. An increased risk of developing lymphoproliferative cancers was found among both women and men with RA in a large study (45). Similarly, in a meta-analysis of 21 publications from 1990 to 2007 on the risk of malignancy in patients with RA, the risk of lymphoma was increased approximately two-fold standardized incidence ratio (SIR) (2.08, 95% confidence interval (CI)=1.8, 2.39) (46). The possible mechanisms for increased risk of hematological cancers in RA include the persistent immune stimulation, the decreased number and function of suppressor T-cells and the decreased activity of natural killer cells in the synovial fluid, tissue, blood and lymph (47). According to a

Table III. Literature review of cancer risk in RA and SS (2006-2014).

<table>
<thead>
<tr>
<th>Reference Author/ Year</th>
<th>ARDs</th>
<th>Country</th>
<th>RR of malignancies</th>
<th>Lymphomas</th>
<th>Carcinomas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lung cancer</td>
<td>Colorectal cancer</td>
</tr>
<tr>
<td>Zhang/2010 (6)</td>
<td>SS</td>
<td>China</td>
<td>48.1</td>
<td>N/A</td>
<td>2.12</td>
</tr>
<tr>
<td>Anderson/2009 (29)</td>
<td>SS</td>
<td>USA</td>
<td>1.9</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Anderson/2009 (29)</td>
<td>RA</td>
<td>USA</td>
<td>1.2</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Solans-Laqué/2011 (30)</td>
<td>SS</td>
<td>Spain</td>
<td>15.6</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Lazarus/2006 (32)</td>
<td>SS</td>
<td>UK</td>
<td>37.5</td>
<td>N/A</td>
<td>2.63</td>
</tr>
<tr>
<td>Parikh-Patel/2009 (45)</td>
<td>RA</td>
<td>USA, California</td>
<td>2.1 (Men) 1.4 (Women)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Smitten/2008 (46)</td>
<td>RA</td>
<td>USA, South America, Europe, Australia, New Zealand</td>
<td>2.08</td>
<td>1.63</td>
<td>0.77</td>
</tr>
<tr>
<td>Hellgren/2010 (48)</td>
<td>RA</td>
<td>Sweden</td>
<td>1.8</td>
<td>2.24</td>
<td>1.18</td>
</tr>
<tr>
<td>Askling/2009 (71)</td>
<td>RA</td>
<td>Sweden</td>
<td>2.7</td>
<td>1.48</td>
<td>0.74</td>
</tr>
<tr>
<td>Mercer/2013 (72)</td>
<td>RA</td>
<td>UK</td>
<td>3.1</td>
<td>2.39</td>
<td>0.96</td>
</tr>
<tr>
<td>Dreyer/2013 (73)</td>
<td>RA</td>
<td>Denmark</td>
<td>2.3</td>
<td>1.67</td>
<td>0.53 (colon) 1.53 (rectal)</td>
</tr>
<tr>
<td>Weng/2012 (74)</td>
<td>SS</td>
<td>Taiwan</td>
<td>3.1 (Men) 7.1 (Women)</td>
<td>1.23 (Men) 1.40 (Women)</td>
<td>0.22 (colon) 0.61 (rectal)</td>
</tr>
<tr>
<td>Johnsen/2013 (75)</td>
<td>SS</td>
<td>Norway</td>
<td>9.0</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Liang/2014 (76)</td>
<td>SS</td>
<td>Meta-analysis</td>
<td>13.8</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

ARCs, Autoimmune rheumatic diseases; SS, Sjögren’s syndrome; RA, rheumatoid arthritis; RR, relative risk; N/A, not available; USA, United States of America; UK, United Kingdom.
In conclusion, in this article we presented our experience in a cohort of autoimmune patients who developed hematological malignancies and solid tumors during their disease evolution. In a period of 33 years, 14 patients with RA and SS developed cancer. Eight developed lymphomas and the rest various epithelial carcinomas. We also extensively discussed the possible carcinogenic effect of anti-autoimmune treatment.

References


Received July 1, 2014
Revised August 5, 2014
Accepted August 7, 2014