Cancer Diagnosis in a Cohort of Patients with Sjogren's Syndrome and Rheumatoid Arthritis: A Single-center Experience and Review of the Literature

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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-κB) appears to be a key connecting element between inflammation and cancer (16). NF-κB 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.

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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

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

Case	Cancer histology	Preexisting ARD	Gender	Age at diagnosis		ARD severity	Tumor stage
				ARD	Cancer		
L.A.	DLBCL	RA, SS	Female	27	57	Severe	Stage II
P.E.	DLBCL	RA	Male	40	62	Severe	Stage II
R.A.	DLBCL	RA	Male	49	58	N/A	Stage IV
S.C.	DLBCL	SS	Male	42	68	Moderate	Stage IV
S.G.	DLBCL	SS	Female	N/A	N/A	N/A	Stage IV
S.R.	Nodular sclerosis Hodgkin's lymphoma	SS	Female	N/A	N/A	N/A	Stage IIIBs
T.T.	Extranodal marginal zone lymphoma	SS	Male	47	67	Moderate	Stage IV
A.A.	Ductal carcinoma in situ of the breast	RA	Female	50	62	Moderate	Stage 0, grade II
T.A.	Lung carcinoid tumor	RA	Female	54	70	Moderate	T1bN0M0, stage IA
F.K.	Hepatocellular Carcinoma	RA	Male	46	65	Moderate	Stage IV
V.F	Colon carcinoma	RA	Male	N/A	N/A	N/A	TxNxM1, stage IV
P.M.	Clear cell renal cell carcinoma	RA	Female	22	52	Moderate	T1bN0M0, stage I, grade III
H.A.	Clear cell renal cell carcinoma	RA	Female	55	56	Moderate	T1aN0M0, stage I, grade III
B.E.	Clear cell renal cell carcinoma	RA	Female	45	72	Moderate	T1aN0M0, stage I, grade III

ARDs, Autoimmune rheumatic diseases; DLBCL, diffuse large B-cell lymphoma; SS, Sjogren's syndrome; RA, rheumatoid arthritis; N/A, not available.

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%). The median age at RA diagnosis was 43.1 (range=22-55). Six were females. The median time from the diagnosis of RA to the development of malignancy was 18.4 years (range=1-30 years). The median follow up was 53.4 months (range=3-132 months). Concerning anti-rheumatic treatment, eight patients received methotrexate and seven anti-TNF agents *i.e.* infliximab. SS patients with malignancy had a median age at SS diagnosis of 38.7 years (range=27-47 years) and three of them were females. The median time from SS diagnosis to cancer detection was 25.3 years (range=20-30 years). One patient had localized and the rest extensive disease. Only two patients were treated with methotrexate. The median follow-up was estimated to be 34 months (2-63 months). All data are presented in Tables I and II.

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 IIIBs, 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 II. *Treatment and survival characteristics*.

Case	Cancer histology	Elapsed time from ARDs to cancer (years)	Treatment of the ARDs	Cancer treatment	Survival from cancer diagnosis (months)
L.A.	DLBCL	30	D-penicillamine, corticosteroids, methotrexate, cyclosporine, infliximab, adalimumab	6 cycles R CEOP	21
P.E.	DLBCL	22	Corticosteroids, methotrexate, gold, D-penicillamine, cyclosporine, leflunomide, infliximab, rituximab	6 cycles R CEOP continued by rituximab (weekly administration)	76
R.A.	DLBCL	9	Corticosteroids, methotrexate	8 cycles R CHOP	63
S.C.	DLBCL	26	N/A	R CEOP	2 (death)
S.G.	DLBCL	N/A	Corticosteroids, methotrexate	8 cycles R CEOP	63
S.R.	Nodular sclerosis Hodgkin's lymphoma	N/A	N/A	8 cycles ABVD	60
T.T.	Extranodal marginal zone lymphoma	20	Corticosteroids, hydroxychloroquine, rituximab	Rituximab (weekly administration for a month and monthly thereafter for a total of 6 months)	24
A.A.	Ductal carcinoma *in situ* of the breast	12	Corticosteroids, methotrexate, hydroxychloroquine, leflunomide, cyclosporine, infliximab	Adjuvant Tamoxifen	61
T.A.	Lung carcinoid tumor	16	Corticosteroids, cyclosporine, methotrexate, infliximab, abatacept	Surveillance	15
F.K.	Hepatocellular Carcinoma	19	Corticosteroids, methotrexate, hydroxychloroquine, leflunomide, cyclosporine, infliximab	Sorafenib	3 (death)
V.F	Colon carcinoma	N/A	Methotrexate, abatacept, corticosteroids	Best supportive care	N/A (death)
P.M.	Clear cell renal cell carcinoma	30	Hydroxychloroquine, corticosteroids, methotrexate, infliximab, salazine, cyclosporine	Just left nephrectomy	24
H.A.	Clear cell renal cell carcinoma	1	Corticosteroids, cyclosporine, methotrexate, leflunomide, infliximab, rituximab, tocilizumab	Just left nephrectomy	132
B.E.	Clear cell renal cell carcinoma	27	D-penicillamine, corticosteroids	Surveillance	N/A

ARDs, Autoimmune rheumatic diseases; DLBCL, diffuse large B-cell lymphoma; N/A, not available; R CEOP, rituximab, cyclophosphamide, etoposide, vincristine, prednisone; R CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; ABVD, adriamycin, bleomycin, vinblastine, dacarbazine.

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

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

Reference Author/ Year	ARDs	Country	RR of malignancies			
			Lymphomas	Carcinomas		
				Lung cancer	Colorectal cancer	Breast cancer
Zhang/2010 (6)	SS	China	48.1	N/A	2.12	N/A
Anderson/2009 (29)	SS	USA	1.9	N/A	N/A	N/A
Anderson/2009 (29)	RA	USA	1.2	N/A	N/A	N/A
Solans-Laqué/2011 (30)	SS	Spain	15.6	N/A	N/A	N/A
Lazarus/2006 (32)	SS	UK	37.5	N/A	2.63	N/A
Parikh-Patel/2009 (45)	RA	USA, California	2.1 (Men) 1.4 (Women)	N/A	N/A	N/A
Smitten/2008 (46)	RA	USA, South America, Europe, Australia, New Zealand, Japan	2.08	1.63	0.77	0.84
Hellgren/2010 (48)	RA	Sweden	1.8	2.24	1.18	0.89
Askling/2009 (71)	RA	Sweden	2.7	1.48	0.74	0.83
Mercer/2013 (72)	RA	UK	3.1	2.39	0.96	1.07
Dreyer/2013 (73)	RA	Denmark	2.3	1.67	0.53 (colon) 1.53 (rectal)	0.89
Weng/2012 (74)	SS	Taiwan	3.1 (Men) 7.1 (Women)	1.23 (Men) 1.40 (Women)	0.22 (colon) 0.61 (rectal)	0.99
Johnsen/2013 (75)	SS	Norway	9.0	N/A	N/A	N/A
Liang/2014 (76)	SS	Meta-analysis	13.8	N/A	N/A	N/A

ARDs, Autoimmune rheumatic diseases; SS, Sjogren's syndrome; RA, rheumatoid arthritis; RR, relative risk; N/A, not available; USA, United States of America; UK, United Kingdom.

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, in our series of patients with SS, 1 among 5 who diagnosed with lymphomas was determined with MALT type. However, 3 of them developed DLBCL, which is in accordance with the literature. The latency period between the onset of the SS and the time of the lymphoma diagnosis was 65 months (31). This period of time is much more prolonged in our experience with a median time of 25.3 years from the diagnosis of SS to the development of the lymphoma (range=20-30 years) (Table II). Gender differences in risk have not been robustly evaluated due to the heavy predominance of female patients in SS (8, 34-38). In our cases the females patients were 3 out of 5. Established risk factors for predicting lymphoma development in SS patients include lymphadenopathy, parotid enlargement, splenomegaly, peripheral neuropathy, purpura or skin vasculitis (5, 39). Recent laboratory findings have shown that cryoglobulinemia, low complement levels of C4 and C3 and lymphocytopenia are suggested risk factors (8, 40). Some viruses (Epstein–Barr virus (EBV), human herpes virus (HHV-8) (41, 42) and bacteria (*H. pylori*, *Chlamydia psittaci*) (43, 44) have been proposed as possible triggers for NHL development, especially in the MALT-subtype. 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

study, during the first 10 years following diagnosis of RA, the overall RR of lymphoma development was 1.75 (95% CI=1.04-2.96). An increased risk of lung cancer was also observed (48). Patients with RA are at high risk for DLBCL, which has been reported to represent up to two-thirds of the NHLs in patients with RA (49-51). In RA, a clear correlation has been demonstrated between lymphoma risk and features linked to disease severity, such as the presence of Felty's syndrome (52), secondary SS (4), high erythrocyte-sedimentation rate values (3) and erosive joint disease (1, 53). This association is stronger in cases reporting severe RA disease than in those with mild disease, as well as among patients who have positive rheumatoid factor (1, 51). In our series, all 3 patients with RA who developed NHL were identified with DLBCL. Two of them had severe disease, which is in accordance to the literature. We report the presence of renal cancer (3 out of 10) and hepatocellular carcinoma (1 out of 10), which are uncommon secondary malignancies in RA patients.

According to Askling *et al*. there was a moderate increase in the risk of developing lung cancer in patients with RA compared to the general population (54). Cigarette smoking would explain an indirect association between RA and lung cancer as smoking is an independent risk factor for both conditions. The mortality from pulmonary disease in RA is approximately twice that of the general population (55). Our report adds one more case of pulmonary carcinoid tumor as a secondary malignancy in patients with RA.

The explanation for the reduced risk of colorectal cancer is most likely due to the increased use of NSAIDs and cyclooxygenase-2 (COX-2)-selective inhibitors by patients with RA (46). A meta-analysis of randomized controlled trials and observational studies concluded that COX-2 inhibitors and NSAIDs reduce the incidence of colonic adenomas and that NSAIDs also reduce the incidence of colorectal cancer (56).

Numerous immunosuppressive drugs have been used to treat ARDs. Some of these agents may directly or indirectly be associated with the subsequent development of malignancies. Among traditional immunosuppressive drugs only cyclophosphamide was found to be definitely carcinogenic with an increased risk of hematologic malignancies (57).

Disease-modifying anti-rheumatic drugs, including methotrexate, azathioprine and other immunosuppressive substances have been repeatedly suggested as a risk factor for RA-associated lymphomas (58-60). However, studies with detailed information on markers of inflammatory activity, as well as treatment (1, 3, 53, 61), did not substantiate the proposed treatment-related increase in lymphoma risk, with the possible exception of azathioprine (1, 62-64). Nevertheless, sustained clinical activity of RA may be the primary risk factor for secondary malignancies and methotrexate may have a net beneficial effect in this respect (51, 61, 65).

In addition, there has been a debate whether biological agents, predominantly TNF inhibitors, would or would not increase the risk for the development of malignancies, primarily lymphomas. In a meta-analysis published in 2012, Solomon *et al*. did not demonstrate increased incidence of cancer development related to the use of biological agents (66). Similarly, Askling and colleagues (54) presented SIRs for various solid tumors and reported no difference in patients with RA who received anti-TNF medication compared with the general population for lung and colorectal cancer. A meta-analysis of randomized clinical trials from 2009 found that the use of etanercept for 12 weeks or more in patients with RA was associated with a non-significant increase in the incidence of cancer (67). Similar overall rates of cancer as in the general RA population was found in patients treated with abatacept that inhibits T-cell activation (68). A recent study found no increase in the overall cancer rate in patients treated with rituximab, a chimeric monoclonal antibody against the protein CD20, compared to those treated with disease-modifying anti-rheumatic drugs (69, 70). Nevertheless, in our series 2 out of 3 patients with RA who developed lymphoma were treated with TNF antagonists. We also report 6 from a total of 7 patients with RA, treated with anti-TNF drugs who developed solid tumors.

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.

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