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Investigation of the Accompaniment of Cancer in Rheumatic Diseases in Mashhad, Iran, from 2007-2018: A Retrospective, Descriptive, Cross-Sectional Study

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Abstract

Background: The present study aimed to investigate the association between rheumatic diseases and cancer in patients referred to two medical-training centers and private clinics over 10 years in Mashhad, Iran.

Methods: This study, which was retrospective, descriptive, and cross-sectional in nature, involved 1,036 rheumatic patients who were referred to Imam Reza and Ghaem Hospitals, as well as rheumatology clinics in Mashhad, Iran, between 2007 and 2018. For each patient, data was collected on demographics, laboratory results, type of rheumatic disease, duration of the disease, frequency of malignancy among rheumatic patients, type of malignancy, and the drug treatments administered up until the final diagnosis of malignancy. The study concluded with a comparison between rheumatic patients with malignancy and those without.

Results: The incidence of malignancy was found to be higher in women ($p=0.005$) and in older age groups ($p=0.005$). Furthermore, patients with malignancy were observed to use biological drugs ($p=0.001$), Adalimumab ($p=0.02$), and Infliximab ($p=0.01$) less frequently. Upon examination of laboratory data, it was noted that the Erythrocyte Sedimentation Rate (ESR) was higher in cases of malignancy ($p<0.005$), while the serum hemoglobin level was lower in such cases ($p=0.009$).

Conclusion: The study's findings suggest a higher incidence of malignancy was observed in women and older age groups. Additionally, patients with malignancy were less likely to use biological drugs, including Adalimumab and Infliximab. These insights could potentially guide future research and therapeutic strategies in the management of rheumatic diseases.

Keywords: Adalimumab, Infliximab, Neoplasms, Rheumatic diseases

Introduction

Rheumatic Diseases (RDs), which are chronic inflammatory conditions that can damage multiple organs, are caused by immune dysfunction. In the absence of an immune response, cancer cells can evade cancer surveillance (1). Furthermore, inflammation may increase the risk of precancerous cells developing into clinically significant cancers, accompanied by the production of cytokines and growth factors (2). In healthy individuals, immunological checkpoints function to promote self-antigen tolerance, thereby reducing autoimmunity and damage to healthy tissues. Several types of tumors exploit these T cell inhibitory pathways as immune escape mechanisms to evade activated cytotoxic T cells (3).

Researchers propose that there is a bidirectional link between autoimmune diseases and cancer. On one hand, numerous autoimmune diseases have been associated with an elevated risk of both hematological and non-hematological malignancies. On the other hand, certain cancers can increase an individual's susceptibility to autoimmune diseases. Additionally, some tumors may display clinical features that are similar to those of autoimmune diseases (4). This could potentially be explained by the underlying immune dysfunction and the degree of organ damage (5,6). A connection between malignancy and Rheumatoid Arthritis (RA) has been identified in several studies (7-9). For instance, paraneoplastic syndromes may present rheumatic clinical signs two years prior to the diagnosis of cancer or its recurrence (10,11). Moreover, it has been observed that breast cancer patients who are administered Aromatase Inhibitors (AIs) are at an increased risk of developing rheumatic diseases, particularly RA (12).

Generally, patients with malignancies may exhibit arthritic symptoms due to a variety of factors, such as the direct invasion of the synovium, soft tissues, or bone by the primary or secondary tumor (13). Relevant studies have underscored the potential for malignancy in patients with RDs, attributing this to autoimmune pathogenesis, shared etiology, and the use of anti-rheumatic medications. These medications, which include biologics and Disease-Modifying Antirheumatic Drugs (DMARDs), may disrupt normal immunosurveillance, thereby heightening the risk of malignancy (14,15).

Numerous studies have highlighted the role of anti-rheumatic drugs in elevating the risk of cancer in patients with rheumatic diseases. Consequently, this has become a critical consideration in the treatment of these patients. Given these concerns, the current study was designed to evaluate the relationship between cancer and RDs diagnosed in patients who were either admitted to the rheumatology departments of hospitals or referred to outpatient rheumatology clinics in Mashhad. The ultimate goal is to establish suitable treatment guidelines.

Materials and Methods

This cross-sectional study was conducted based on a retrospective design. To conduct this study, we analyzed the medical records in the health information system of "Ghaem Hospital" and "Emam Reza Hospital", as well as patients' files in privet rheumatology clinics in Mashhad over 10 years (2007-18).

Study design and sampling

All patients with a definitive RD diagnosis based on relevant criteria were included in the study. The patients who developed malignancy after RD and in the course of the disease were included in the malignant group and others in the non-malignant group. Demographic data, including age and gender, laboratory data, paraclinical pathology data, and time between the onset of rheumatic symptoms and cancer diagnosis, were collected for each patient. Also, patients were categorized based on rheumatic manifestation or primary diagnosis based on the history recorded in the file. These categories are: the type of RD, the duration of the disease, and the frequency of cancer in diagnosed rheumatic patients. In addition, the drug treatments received until the final cancer diagnosis were recorded and categorized. The data of the patients who were discharged with confirmation of malignancy were collected by referring to their medical records.

Inclusion and exclusion criteria

All patients who had a definitive diagnosis of RD based on relevant criteria were included in this study. RD included RA, seronegative spondyloarthropathies (including psoriatic arthritis, reactive arthritis,

ankylosing spondylitis, enteropathic arthritis), systemic sclerosis, Sjogren's syndrome, dermatomyositis/polymyositis, Systemic Lupus Erythematosus (SLE) and antiphospholipid syndrome, vasculitis, including vasculitis of large vessels (Janet's tuberculosis and polymyalgia rheumatica-Takayasu), vasculitis of medium vessels (pan-classical), small vessels (Wegener-Church-Strauss-panmicroscopic-cryo) Behcet, oncogenic osteomalacia, Still's disease and sarcoidosis).

The patients who did not have evidence of malignant pathology according to subsequent follow-up and those who could not be reached through follow-up and phone calls were excluded from the study.

Data analysis

The obtained data were analyzed in SPSS software version 24 (IBM Corp., Armonk, NY, USA). To evaluate data normality, the Kolmogorov-Smirnov test was utilized. Mean and standard deviation were used to describe quantitative data, while frequency and percentage were employed for qualitative variables. Statistical analysis was performed using the t-test, and its non-parametric equivalent Mann-Whitney U. Categorical data were evaluated using the Chi-square test. A p-value less than 0.05 was considered significant.

Ethical considerations

The present study was extracted from a thesis to obtain a doctorate in rheumatology (Code: T5398). A study protocol has been approved by the Ethics Committee of Mashhad University of Medical Sciences, Mashhad, Iran (IR.MUMS.MEDICAL.REC.1398.255). Patient data were entered into checklists anonymously to maintain confidentiality.

Results

In general, 1036 patients with RDs were included. All patients belonged to the Iranian-Asian ethnic group. Of these, 136 cases (13.1%) had malignancy, and 900 patients (86.9%) had no malignancy. In terms of gender, 225 (21.7%) participating patients were male, and 811 (78.3%) cases were female. The highest frequency of malignancy was reported in women, with 119 (87.5%) cases. There was a statistically significant difference between patients with and without malignancy (χ^2=0.002; p=0.005). The time interval between diagnoses of RDs to malignancy diagnosis was 5.96±5.82 years (a range of 1-25 years). The mean age of patients was 51.53±15.23 years (age range: 13-94 years). The mean age of patients with malignancy was higher than that of the group without malignancy, which was statistically significant (Z=-6.28; p<0.001). Table 1 displays the mean of patients' clinical and laboratory information. Based on the obtained results, in the measurement of Erythrocyte Sedimentation Rate (ESR) between patients with and without malignancy, a significant difference was observed, and it was significantly higher in people

Table 1. Demographic and laboratory information of patients

Variables		Malignancy		No Malignancy		Total		Z	p-value
		Mean	SD	Mean	SD	Mean	SD		
Age		59.01	12.6	50.41	15.28	51.53	15.23	-6.28	<0.001
Gender (N/%)	Male	17/ 12.5		208/23.1		225/21.7		–	–
	Female	119/ 87.5		692/ 76.9		811/ 78.3			
Duration of rheumatic disease (years)		9.62	7.06	9.06	5.06	9.14	5.36	-1.76	0.071
Erythrocyte sedimentation rate (*mm/hr*)		31.68	26.25	21.26	19.16	22.68	20.57	-4.84	<0.001
Lactate dehydrogenase (mg/*dL*)		351.61	125.22	338.20	120.32	340.12	121.03	-1.03	0.301
Hemoglobin (*g/dL*)		12.65	1.67	13.11	1.65	13.05	1.66	12.61	0.009

with malignancy (Z=-4.84; p<0.001). In addition, hemoglobin levels were significantly lower in patients with malignancy than those without malignancy (Z=-2.61; p=0.009). There was no significant difference in the mean Lactate Dehydrogenase (LDH) level between the two groups.

The frequency of clinical manifestations of patients is illustrated in table 2. It should be noted that the clinical manifestations were documented for each patient during the period of the onset of rheumatic manifestations and cancer diagnosis. According to the recorded reports, a significant difference was observed between the two groups in terms of clinical manifestations (p<0.001). Comorbidity was reported in 45.4 and 52.2% of patients with and without malignancy, respectively (p=0.62). The examination of the amount of medicine consumed in rheumatic patients indicated that patients without malignancy consumed more biological medicines (p=0.001), Infliximab (p=0.01), and Adalimumab (p=0.02) compared to their counterparts with malignancy. No significant difference was observed between the two groups in the consumption of other medicine categories (Table 3). Moreover, the frequency of the type of RD is illustrated in table 4.

The obtained results revealed a significant difference between the two groups in terms of the RD type (p=0.031). Table 5 depicts the frequency of RDs in each type of cancer. Moreover, the results showed no significant correlation between the type of RD and the type of cancer (r= -0.03; p=0.73). In total, the results of logistic regression analysis in examining the rate of malignancy in RA patients compared to other diseases indicated that the type of RDs could not be predictive of malignancy in patients with RDs (Ratio: 2.1; 95%CI: 1-1.08; p=0.051). Furthermore, based on logistic regression, elevated chance of malignancy demonstrated no significant relationship with an increase in age (Ratio: 1.3; 95%CI: 0.94-0.97; p<0.001); clinical manifestations (Ratio: 1.1; 95%CI: 088-0.99; p=0.02), and ESR level (Ratio: 1.4; 95% CI: 0.97-0.99; p<0.001).

Discussion

As evidenced by the results of this study, the frequency of malignancy was 13.1% among patients with RDs, and the highest frequency of malignancy was reported in women. A significant

Table 2. Frequency of clinical manifestations of rheumatic patients

Clinical criteria	Without Malignancy		Malignancy		Total	
	No	%	No	%	No	%
Skin lesion	87	9.7	2	1.5	89	8.6
Arthritis/arthralgia	398	44.2	32	23.5	430	41.5
Muscle weakness	20	2.2	1	0.7	21	2
Low back pain/bone pain	80	8.9	24	17.6	104	10
Fever, sweating, weight loss/anorexia	18	2	20	14.7	38	3.7
Leukocyte alkaline phosphatase/organomegaly	1	0.1	16	11.8	17	1.6
Mass	-	-	10	7.4	10	1
Cough/dyspnea/hemoptysis	51	5.7	7	5.1	58	5.6
Dysphagia	3	0.3	2	1.5	5	0.5
Others	242	26.9	22	16.2	264	25.5
Total	900	100	136	100	1036	100

Table 3. Frequency of using different medicines in rheumatic patients

Variables		Without malignancy		Malignancy		χ^2	p-value
		No	%	No	%		
Biological medicines	YES	191	21.2	13	9.6	10.16	0.001
	No	709	78.8	123	90.4		
Cytotoxic drugs	YES	258	28.7	37	27.2	0.12	0.72
	No	642	71.3	99	72.8		
Hydroxychloroquine	YES	373	41.4	63	46.3	1.15	0.28
	No	527	56.6	136	56.7		
Prednisolone	YES	723	80.3	114	83.8	0.607	0.33
	No	177	19.7	22	16.2		
Methotrexate	YES	48	35.3	88	64.7	-	0.43
	No	349	38.8	44	35.3		
Mycophenolate mofetil	YES	76	8.4	10	7.4	0.18	0.66
	No	824	91.6	126	92.6		
Azathioprine	YES	209	23.2	30	22.1	0.09	0.76
	No	691	76.8	106	77.9		
Cyclophosphamide	YES	53	5.9	11	8.1	0.98	0.32
	No	847	94.1	125	91.9		
Cyclosporine	YES	26	2.9	3	2.2	0.203	0.65
	No	874	97.1	133	97.8		
Rituximab	YES	51	5.7	4	2.9	1.74	0.18
	No	849	94.3	132	97.1		
Infiliximab	YES	54	6	1	0.7	6.51	0.01
	No	846	94	135	99.3		
Etanercept	YES	70	7.8	6	4.4	1.96	0.16
	No	830	92.2	130	95.6		
Adalimumab	YES	85	9.4	5	3.7	4.95	0.02
	No	815	90.6	131	96.3		

difference was observed between the two groups of malignancy and those without malignancy in terms of clinical manifestations. In addition, the ESR level is significantly higher in patients with malignancy and RDs. Conversely, the blood hemoglobin level is significantly lower in these patients. Another remarkable finding of our study was the lower consumption of biological medicines, Adalimumab,

Table 4. the frequency of type of rheumatic disease in patients with and without malignancy

Type of rheumatic disease	Malignancy		Without malignancy	
	No	%	No	%
Rheumatoid Arthritis (RA)	55	40.4	261	29
Systemic Lupus Erythematosus (SLE)	11	8.1	91	10.1
Scleroderma	5	3.7	31	3.4
Sjögren Syndrome (SS)	2	1.5	37	4.1
Behçet's Disease (BD)	4	2.9	40	4.4
Vasculitis	9	6.6	55	6.1
DM/PM	4	2.9	18	2.0
Seronegative spondyloarthropathies (SpA)	15	11.0	138	15.3
Overlap Syndrome	19	14.0	121	13.4
Sarcoidosis	1	0.7	23	2.6
Polymyalgia Rheumatica (PMR)	3	2.2	8	0.9
Other Myositis	2	1.5	3	0.3
Relapsing Polychondritis (RP)	2	1.5	1	0.1
Crystal Arthropathies	2	1.5	26	2.9
SLE+APS	1	0.7	24	2.7
Others	1	0.7	23	0.26

Table 5. Frequency of types of rheumatic diseases in each type of cancer

Type of disease	Rheumatoid arthritis	Systemic lupus erythematosus	Scleroderma	Sjogren's syndrome	Behcet's disease	Vasculitis	Polymyositis (PM)/ Dermatomyositis (DM)	Seronegative spondyloarthropathy	Overlap syndrome	Sarcoidosis	Polymyalgia rheumatica	Other myositis	Relapsing polychondritis	Crystal arthropathies	Antiphospholipid syndrome	IgG4 syndrome	Total
Breast Cancer	15	3	2	1	0	1	0	4	4	0	1	0	1	0	0	0	32
Multiple myeloma	8	0	0	0	0	1	0	2	3	1	2	0	0	1	1	1	20
Thyroid cancer	1	4	0	0	2	2	0	2	5	0	0	0	0	0	0	0	16
Uterine/cervical cancer	4	1	0	0	1	0	1	1	1	0	0	0	1	0	0	0	10
Brain Tumor	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
Nasopharyngeal carcinoma	3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	4
neuroendocrine tumor	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Esophageal cancer	4	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	4

Contd. table 5

Gastric cancer	2	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	4
Colon cancer	5	0	0	0	0	0	1	0	3	·	·	·	·	·	·	·	9
Transitional cell cancer	2	0	0	0	0	1	2	1	0	0	0	1	0	0	0	0	7
Leukemia	1	0	0	1	0	1	0	1	2	·	·	·	·	·	·	·	6
Lymphoma	2	2	0	0	0	0	0	1	1	0	0	1	0	·	·	·	7
Throat cancer	1	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	1
Lung cancer	1	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	1
Joint tumor	0	0	2	·	·	·	·	·	·	·	·	·	·	·	·	·	2
Uterine+ breast cancers	0	0	0	0	1	·	·	·	·	·	·	·	·	·	·	·	1
Breast cancer + multiple myeloma	1	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	1
Breast + pancreatic cancers	0	0	1	·	·	·	·	·	·	·	·	·	·	·	·	·	1
Ovarian cancer	3	0	0	0	0	0	0	2	·	·	·	·	·	·	·	·	5
Prostate +colon cancers	0	0	0	0	0	1	·	·	·	·	·	·	·	·	·	·	1
Basal cell carcinoma	1	0	0	0	0	1	·	·	·	·	·	·	·	·	·	·	2
Total	55	11	5	2	4	9	4	15	19	1	3	2	2	2	1	1	136

and Infliximab in patients with malignancy.

Based on logistic regression analysis, the type of RD could not be predictive of malignancy in patients with RD. Adjusted logistic regression in the presence of age, gender, and comorbidities pointed to the significant relationship of an elevated chance of malignancy with an increase in age, clinical manifestations, and ESR level. The majority of studies on the relationship between rheumatic and malignant diseases in the literature focus on the emergence of malignant diseases in RD patients. For instance, several studies have revealed that several systemic inflammatory rheumatic disorders, such as RA, SLE (5), Systemic Sclerosis (SS) (16), and Ankylosing Spondylitis (AS) (17), are associated with an increased risk of acquiring different malignancies.

Moreover, there has been evidence that RA is an independent risk factor for the development of malignancies, especially lymphoma and lung cancer (18,19). According to some studies, the rising prevalence of inflammatory rheumatic diseases, particularly RA, may be explained by the existence of genetic pathways that contribute to both an inclination toward cancer and the tendency toward autoimmunity (20). Researchers found that nearly a third of breast cancer patients developed inflammatory RDs after diagnosis (21). Inflammatory RDs associated with RA were more frequent than primary Sjögren Syndrome, psoriatic arthritis, SS, gout, Behçet's Syndrome, SLE, AS, and non-radiographic axial spondyloarthropathy, which were less frequent.

Based on the acquired findings in this study, the most prevalent occurrence of breast cancer was observed in 31 cases, accounting for 23.1% of the total. Furthermore, there was an occurrence of breast cancer coexisting with uterine cancer (0.7%), breast cancer coexisting with multiple myeloma (0.7%), and breast cancer coexisting with pancreatic cancer (0.7%) among the patients (19). However, it should be mentioned that in addition to the possibility of

malignant diseases developing during the course of systemic RD, people with breast cancer may also experience the opposite situation. It should be noted that motor symptoms in breast cancer patients might also be indicative of concomitant rheumatic disorders, in addition to being brought on by bone metastases or paraneoplastic effects.

A study revealed that the prevalence rates of RA among Turkish females aged 45-54, and 55-64 years, both close to the mean age of breast cancer patients included in their study, were 0.77 and 0.88%, respectively (21). As mentioned, the results of the current research are not consistent with the data of similar studies. In general, obtained results demonstrated that the frequency of patients with RA is higher than other RDs. Moreover, in the present research, RA patients had the greatest incidence of breast cancer among rheumatic patients. Furthermore, in patients with RA, multiple myeloma (n=8) was associated with the second kind of cancer. Therefore, a regression test to investigate the relationship between malignancy and presence of rheumatoid arthritis was performed. This test showed that RA could not predict the occurrence of malignancy among patients. Furthermore, one of the important points raised in relation to this issue is that higher disease activity and impaired physical function are commonly observed in elderly patients suffering from RDs (22).

The results of this study also strongly indicated that age is one of the factors affecting the accompaniment of malignancy in rheumatic patients (23). Secondly, due to the existence of chronic inflammation and poor DNA repair, the immunological aging process in RA may increase the likelihood of developing this condition (24). One of the other noteworthy points is that an early characteristic of RA has inappropriately accelerated immunosenescence, which occurs regardless of the length of the disease course (25). Moreover, as compared to age-matched healthy individuals, RA patients have premature declines in thymic output, loss of T cell diversity, and T cell aging (26).

The assessment of the medications used in the treatment of rheumatic patients and the risk of cancer was another part of our study. Anti-TNF drugs stop Tumor Necrosis Factor (TNF) from acting in its extracellular and membrane forms, which is thought to play a significant role in the pathogenesis of RA (27). It is controversial whether immunosuppressant therapy for RA increases the risk of cancer.

According to the literature review, both conventional synthetic Disease-Modifying Anti-Rheumatic Drugs (csDMARDs) and biological Disease-Modifying Anti-Rheumatic Drugs (bDMARDs) are generally safe with regard to malignancy; however, melanoma may present a slight risk (28). The present study pointed out that the use of biological drugs, Adalimumab, and Infliximab was higher in patients without malignancy than in patients with malignancy. By binding to TNF α, Adalimumab offers treatment for RA. For instance, researchers found that Adalimumab has a favorable risk-benefit ratio when administered to Taiwanese RA patients (29). In general, according to the information obtained in the current study, which strengthens the relationship between the use of biological drugs and the reduced risk of cancer in rheumatic patients, it can be suggested that the use of biological drugs reduces the activity of the RD. Moreover, as a result, it significantly reduces one of the influential factors in cancer risk.

In the study by Fagerli *et al*, conducted on 709 patients who received biological treatment, nonmelanoma skin cancer incidence increased considerably overall and in women (30). Nevertheless, some scientists mentioned that imputed predictions of the likelihood of developing a clinically detectable malignancy in the subsequent 6-12 months of monitoring, based on the frequency of occurrences in the general population, may be inaccurate (27). In general, 78.3% of the examined patients in our study were female. Accordingly, the incidence of cancer in females was significantly higher. In Iran, the adjusted data showed 35.9% of men against 52.8% of women (31).

The most frequent reasons for high ESR values in the study population of Bitik were newly diagnosed RD, infection, and malignancy (32). In addition, a study by Nikiphorou, who investigated clinical manifestations and comorbidity in the first manifestations of RA before DMARDs, demonstrated that ESR fell and hemoglobin rose over time after treatment at the time of assessment was taken into account (33). However, there is a dearth of studies on the relationship between ESR and HB levels in rheumatic patients with cancer.

Conclusion

The results of this study suggest that the relationship between rheumatic disorders and cancer is affected by such characteristics as gender, age, and drug type. In comparison to other rheumatic disorders, RA is associated with a higher rate of cancer.

Limitations and advantages

Among the notable limitations of the present study, considering the design of the study, we can refer to the lack of other helpful information, such as serological information, disease severity score records, and patients' personal information, such as lifestyle, smoking, family history of malignant diseases, occupational exposures, and body mass index, that can play an influential role in the risk of cancer. In the study groups, multivariate stratified analysis was not performed for cancer risk. Another limitation of this study was the failure to record the death rate of patients. Considering that there is a close relationship between RD and the occurrence of different types of cancer, as well as the type of RD, race and treatment may affect the type and occurrence of different types of cancer in these patients. The present study can be of great help to researchers in obtaining comprehensive instruction to resolve doubts in this field in Iran.

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Conflict of Interest

A financial or other conflicts of interest does not exist between the authors.

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