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Original Article

The Association of Anti-CCP Positivity with Extra-Articular Manifestations in Patients with Rheumatoid Arthritis

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ABSTRACT

Rheumatoid Arthritis (RA) is an autoimmune inflammatory disorder that primarily affects the joints. **Objective:** To examine association between anti-cyclic citrullinated peptide and extra-articular manifestation of Rheumatoid arthritis. **Methods:** It was a descriptive cross-sectional study in the Department of Rheumatology outpatient Khyber Teaching Hospital in Peshawar from 13th April 2023 to 13th September 2023. A descriptive cross-sectional study was conducted on 100 patients diagnosed with rheumatoid arthritis according to ACR/EULAR 2010 criteria at the Rheumatology outpatient department of Khyber teaching hospital in Peshawar from 13th April 2023 to 13th September 2023. Sampling technique was non probability consecutive. Statistical analysis was performed using SPSS version 23.0. **Results:** Our study involved 100 patients diagnosed with rheumatoid arthritis. Majority of the patients were female (90%) with overall mean age was 42.3 ± 10.06 years. The average duration of the disease was 5.9 years, with a mean RA disease activity score of 2.8. Extra-articular manifestations were observed in 84% of the patients, encompassing various symptoms such as anemia, subcutaneous nodules, episcleritis, and interstitial lung disease. Most patients (94%) tested positive for Rheumatoid Arthritis Factor, while 84% tested positive for anti-CCP antibodies. Our analysis revealed significant associations between the presence of extra-articular manifestations and factors such gender distribution, disease activity score and anti-CCP antibody positivity while no significance was noted for factors such as age, Rheumatoid Arthritis Factor and duration of disease. **Conclusions:** Our study concludes that anti-CCP was positively associated with the presence of extra-articular manifestation of Rheumatoid Arthritis.

INTRODUCTION

Rheumatoid arthritis (RA) is commonly associated with the presence of rheumatoid factor (RF), a chronic autoimmune illness that affects both the joints and other regions of the body. Early diagnosis and treatment with disease modifying ant rheumatic drugs (DMARDs) are essential for controlling the disease and preventing joint damage. Finding a trustworthy serological marker or markers is therefore essential for an early and precise diagnosis. Although RF can be positive for a number of viral and autoimmune disorders, its sensitivity for diagnosing RA is only moderate [1]. Rheumatoid arthritis (RA) is a serious health concern; research indicates that it affects 0.5% to 1% of the world's population. Following osteoarthritis and gout as the top causes of disability, RA is listed as well [2]. According to earlier data from Pakistan, Karachi has a 0.142% prevalence of rheumatoid arthritis (RA), with a higher incidence rate in women [3]. One of the classification criteria recommended by the American College of Rheumatology (ACR) is the IgM rheumatoid factor (RF), which is frequently used to diagnose

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rheumatoid arthritis (RA) [4]. Research has demonstrated that autoantibody positivity can be detected up to twenty years before the clinical manifestations of rheumatoid arthritis (RA). Additionally, studies have shown that anti-cyclic citrullinated peptide (anti-CCP) might be positive even in patients with. RA who do not have an RF test. Anti-CCP may therefore be regarded as the recommended course of action for patients who are suspected of having RA [5]. The happening of Reports has indicated that between 17.8% and 40.9% of patients with rheumatoid arthritis (RA) experience extra-articular symptoms (ExRA) [6]. Male gender, certain genetic markers such the HLA-DRB1*04 subtype, antinuclear antibodies (ANA), positive rheumatoid factor (RF), and anti-CCP antibodies, as well as various environmental variables, particularly smoking, are all linked to exaggerated RA (ExRA) in people with RA [7]. In clinical practice, it is essential to recognize and acknowledge the existence of ExRA because it is linked to increased rates of morbidity and mortality [8]. Research findings indicated that patients with ExRA had a 2.5-fold worse mortality rate than those with RA without ExRA [8]. Along with antinuclear antibodies (ANA) and rheumatoid factor (RF), other factors that may be related to ExRA have also been studied: anti-cyclic citrullinated peptide (anti-CCP) antibodies. With frequencies ranging from 55% to 69%, these antibodies are commonly detected in the serum of RA patients [9]. Even more reliable than rheumatoid factor, anti-CCP antibodies are highly specific for RA and indicate the severity of the illness [10]. ExRA, such as serositis and pulmonary fibrosis, has been associated with elevated levels of anti-CCP2 antibodies [11]. A study conducted on menopausal women diagnosed with RA showed that patients with ExRA had a significantly higher frequency of osteoporosis compared to RA patients without these manifestations. This was determined through a retrospective analysis of patient data [12]. SE (Shared Epitope) alleles have been found to be associated with an increased risk for RA, and studies have shown that the presence of SE alleles in RA patients is associated with the presence of anti-CCP antibodies. Interestingly, anti-CCP antibodies have been detected in both SE-positive and SE-negative RA patients, indicating that the presence of SE alleles is not a prerequisite for the development of anti-CCP antibodies [5]. To examine association between anti-cyclic citrullinated peptide and extra-articular manifestation of Rheumatoid arthritis.

METHODS

Descriptive cross sectional study was conducted on patients diagnosed with RA at outpatient department, Rheumatology, Khyber teaching hospital Peshawar, from 13th April 2023 to 13th Sep 2023 and data collection letter was obtained with Reference Number: 5146-5/CRD/KTH. Total of 100 patients were included in the study. 33 patients were excluded based on exclusion criteria. The sampling technique was nonprobability consecutive. Sample size was calculated by WHO sample size calculator. Informed verbal and written consent were taken from every patient. Age, gender, disease duration, and rheumatoid arthritis Disease activity scores 28 (DAS-28) were among the clinical and demographic information gathered from each patient after a thorough assessment. A rheumatologist's clinical evaluations and medical imaging were used to gather information on the existence of ExRA. A pre-made questionnaire was used to collect the data, which was then stored in a safe database for analysis. The inclusion criteria include: 1) individuals diagnosed with rheumatoid arthritis as adults (older than 16 years) based on 2010 selection criteria of the American College of Rheumatology/ European League against Rheumatism (ACR/EULAR); patients tested with anti-CCP antibodies; individuals with history of cardiovascular conditions, interstitial lung disease, and rheumatoid nodules undergo assessment for extra-articular rheumatoid arthritis (ExRA). The exclusion criteria include individuals with medical history of autoimmune diseases, lung conditions like COPD or asthma and patients refused to take part in study. Software for statistical analysis was SPSS version 23.0. In addition to Descriptive statistics, to investigate the relationship between gender, Anti-CCP positivity, and DAS 28, bivariate analysis was employed, and ExRA using appropriate statistical tests, such as chi-square tests or t-tests. A P-value of less than 0.05 will be considered statistically significant for all analyses.

RESULTS

The 100 patients, n=90(90%) were female while n=10(10%) were male. The patients' average age was 42.3 (SD±10.06). The patient's mean illness duration was 5.9 (SD±3.2). The mean RA disease activity score was 2.8(SD±0.54). According to Table 1, patients were divided into age categories, with 55% of patients falling in the 16-40 years range and the remaining 45% being 41 years or above. 84% of patients exhibited ExRA manifestations, while the remaining 16% did not. Further details regarding the type of extra articular manifestations are provided, with varying frequencies such as anemia (6%), anemia with subcutaneous nodules (11%), episcleritis (5%), interstitial lung disease (12%), and others. The table also includes information on the Rheumatoid Arthritis Factor, where 94% were positive and 6% were negative for it. Lastly, the Anti-CCP results indicate that 84% tested positive, while 16% tested negative (Table 1).

Table 1: Clinicodemographic Characteristics among study participants

Variables	Categories	N (%)
Gender of Patient	Male	10 (10.0)
	Female	90 (90.0)
	Total	100 (100.0)

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Age (Years)	16-40yrs	55 (55.0)
	41 or above	45 (45.0)
	Total	100 (100.0)
Presence Extra	Yes	84 (84.0)
	No	16 (16.0)
	Total	100 (100.0)
Type of Extra Articular Manifestation	Anemia	6 (6.0)
	Anemia	22 (22.0)
	Anemia, Subcutaneous Nodule	11 (11.0)
	Anemia, Pleural Effusion	5 (5.0)
	Anemia, Subcutaneous Nodule	6 (6.0)
	Episcleritis	5 (5.0)
	ILD	12 (12.0)
	None	16 (16.0)
	Pericarditis	5 (5.0)
	Scleritis	6 (6.0)
	Subcutaneous Nodule	6 (6.0)
	Total	100 (100.0)
Rheumatoid Arthritis Factor	1	94 (94.0)
	2	6 (6.0)
	Total	100 (100.0)
Anti CCP Results	Positive	84 (84.0)
	Negative	16 (16.0)
	Total	100 (100.0)

The table 2 provided a detailed summary of the variables and their relationships within the study. In the context of the existence of non-articular symptoms, in which 84 patients had these manifestations and 16 did not. In age categories, out of the 55 patients aged 16-40 years, 44 had extra-articular manifestations while 11 did not. In the 41 years or above category, 40 patients had manifestations and 5 did not with the value of 0.176. In gender distribution, out of the 10 male patients, 5 had extra-articular manifestations, while out of the 90 female patients, 79 had them with p value of 0.009. Within the group of patients with extra-articular manifestations, 78 patients tested positive for the RA factor, and 6 patients tested negative. On the other hand, among the patients without extra-articular manifestations, none of them had a positive RA factor result with p value of 0.341. Within the group of patients with extra-articular manifestations, 79 patients tested positive for Anti-CCP, indicating anti-CCP antibodies, whereas five patients had negative test results. On the other hand, among the patients without extra-articular manifestations, 11 patients did not have anti-CCP antibodies, and 5 patients tested positive for Anti*CCP. According to duration of disease, patients with shorter disease durations of 1.5 and 2 years exhibited a 100% prevalence of extra-articular manifestations. Further more, patients with disease durations of 5, 7, and 10 years also showed a high occurrence of these manifestations, ranging from 66.7% to 100% (p value 0.14). Among the total 100 patients, varying scores were observed, with 12 patients (12.0%) having a score of 2.00, 33 patients (33.0%) having a score of 2.50, 27 patients (27.0%) having a score of 3.00, 23 patients (23.0%) having a score of 3.50, and 5 patients (5.0%) having a score of 4.00. Notably, for scores of 3.50 and 4.00, no patients without disease activity were observed (P value=0.001).

Table 2: Comparison of Presence of Extra and Different Variables

Variables	Categories	Presence Extra Articular Manifestation		Total	P-Value
		Yes	No		
Age	16-40 Years	44	11	55	0.176
	41 or above	40	5	45	
Total		84	16	100	
Gender	Male	5	5	10	0.009
	Female	79	11	90	
Total		84	16	100	
Rheumatoid Arthritis Factor	Positive	78	16	94	0.341
	Negative	6	0	6	
Total		84	16	100	
Anti CCP Results		Postive	79	5	<0.001
		Negative	5	11	
Total		84	16	100	
Duration of Disease		1.5 years	11	0	0.14
		2	6	0	
		3.00	17	5	
		5.00	12	0	
		7.00	16	0	
		10.00	22	11	
Total		84	16	100	
RA Disease Activity Score		2.00	6	6	0.001
		2.50	28	5	
		3.00	22	5	
		3.50	23	0	
		4.00	5	0	
		2.00	6	6	
Total		84	16	100	

DISCUSSION

Rheumatology has advanced significantly with the addition of the complementary component of the anti-cyclic citrullinated peptide (anti-CCP) antibody assay ACR/EULAR RA classification criteria [1]. The importance the use of the anti-CCP antibody test in the preliminary identification of ExRA has been the subject of debate in the literature [13]. In this study, the majority of patients diagnosed were in the middle age group, with a higher prevalence among females, which is consistent with similar studies [13-16]. The mean disease activity score in our study was 2.8 (SD 0.53), while Sulaiman FN reported a mean disease activity score of 4.74 [13] Another study reported a mean DAS28 of 6 [14]. It was observed a positive association between gender and ExRA in our study, which differs from the findings of ElSharbini DA, who reported no statistical significance [14]. The frequency of ExRA in our

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study was 84%, whereas other studies reported frequencies of 40.6% and 42.6%, respectively [7, 17]. Anti-CCP antibodies and ExRA were found to be related (p value <0.001). the results of our study differ from the study conducted by De Rycke *et al* [18]. It was found positive association between presence of ExRA and disease activity score, which is line with the finding of Rehman M *et al* [19]. It did not find any significant relationship between the duration of disease and ExRA with a p-value of 0.14. However, a study by Cojocaru M *et al.*, reported a significant association between longer disease duration and the presence of extra-articular manifestations [20]. The study is subjected to few limitations worth mention. First it was cross sectional study. Second, the sample size may be low make a generalize statement. Third, we didn't measure the association between different types of ExRA and antiCCP. Fourth, the consecutive nature of sampling technique might introduce bias in the results. Despite limitations, our study highlights the importance of anti CCP in the management of RA with ExRA.

CONCLUSIONS

This study revealed significant associations between the presence of ExRA and anti-CCP antibody positivity. Furthermore, gender was also positively associated with ExRA along with disease activity score while no association was between duration of disease and presence of extra articular manifestation.

Authors Contribution

Conceptualization: NU, AZ
Methodology: NU, AW, AZ, MR, SA, MI, ZMW
Formal analysis: NU, AZ
Writing, review and editing: NU, AW, AZ

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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