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Diagnosis of Sero-negative Rheumatoid Arthritis Depending on Pathology Associated with Clinical Picture

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Objectives: This study was done to assess the role of synovial tissue analysis in rheumatoid arthritis (RA) patients.
Methods: All data were recorded at baseline. All patients underwent clinical, radiologic, serologic, and histological assessments before treatment. Patients were divided into anti-citrullinated protein antibody (anti-CCP) positive and anti-CCP-negative and were compared according to different disease aspects. Correlations between clinical, laboratory, imaging, histological, and pathophysiological data were done for all patients.

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Results: There were no statistically significant differences in synovial cell infiltrates according to the serology.
Conclusion: Both study groups had similar synovial cell infiltrates.

Keywords: Arthritis; rheumatoid; synovial tissue; synovitis.

1. INTRODUCTION

Increasing evidence suggests that anti-CCP negative rheumatoid arthritis (RA) remains an entity distinct from that of ACPA+ disease with a highly variable disease course [1-3]. This translates to significant challenges in disease management including definitive early diagnosis remains uncertain, adversely affect outcomes in part contributed by the challenges arising from finding an early optimal therapy [4-8]. Thus, biomarkers capable of refining diagnosis and improving on current classification criteria early in the disease course and moreover predicting outcome and treatment response for patients with anti-CCP -ve RA are urgently needed in order to both reduce morbidity and target biologic therapies according to likelihood of response and/or prognosis [9-12] defined by specific synovial cellular and molecular signatures and moreover predict therapeutic response to disease modifying therapy and joint damage progression. Importantly, these pathotypes have also been described in late-stage disease (joint replacement tissue) [13] indicating the potential for such pathotypes may function as disease endotype classifiers.

Secondly, we have demonstrated that synovial pathobiological signatures can improve on current clinical classification criteria of early inflammatory arthritis (RA 2010 ACR/EULAR, RA 1987 and undifferentiated subgroups) through segregating patients according to synovial cellular/molecular signatures and clinical outcome including requirement for biologic therapy at 12 months. From the same PEAC data set preliminary results have also demonstrated that the synovial cell infiltrate (B cells, T cells, macrophages, and plasma cells) in anti-CCP -ve RA is significantly different from anti-CCP +ve patients while more like PsA suggesting shared pathophysiological mechanisms between sero-ve arthropathies and anti-CCP -ve RA. This offers the opportunity to define a new taxonomy of disease for patients with anti-CCP -ve RA and through the identification of specific pathways of inflammation may enable the development of pathology-driven, rather than clinical classification-driven treatment algorithms. Though similar approaches have been tried in the past, mainly by the Amsterdam group [14,15], the smaller number of patients in whom synovial tissues were available (n=69 in total) and the lack of matched molecular analysis in that cohort makes this proposal of critical relevance.

Therefore, the overall aim of this project is to examine in early arthritis patients whether sero -ve RA can be refined at disease initiation according to pathophysiological signatures associated with clinical phenotype.

2. PATIENTS AND METHOD

2.1 Enrollment of the Patients

This study was done on 30 RA patients collected from outpatient clinics diagnosed according to the latest diagnostic criteria of RA [5]. The patients included in this study complained of persistent activity in one joint despite their adherence to treatment.

Written informed consent from all the patients was obtained and all our patients. The patient who was excluded from this study is any patient with bleeding tendencies who received local injections of corticosteroid in the selected joint for synovium analysis in the last 3 months.

2.2 Clinical Classification of Patients

All patients underwent detailed. history taking, joint counting, assessment of disease activity using the degree of tenderness of the injected joint was assessed on a score (0–3). The degree of pain was evaluated by using the visual analog scale (VAS) for pain in the affected joints measured using a ten cm horizontal scale with 10 degrees [16], then clinical classification via EULAR/ACR criteria for RA by exclusion according to revised classification criteria published since the initiation of the study. These included CASPAR criteria for psoriatic arthritis, and ASAS criteria for spondylarthritis.

2.3 Histological Classification

Synovium samples will undergo immunohistochemical staining and patients will be classified according to synovial pathotype, degree of synovitis. Differences in the degree of immune cell infiltration/synovitis within each diagnostic subgroup will be evaluated to look for significant associations between clinical classification and synovial histology. In addition, RA patients cluster according to synovium immune cell infiltration and whether the specific histological classification is reflected in variation in clinical parameters such as autoantibody expression, inflammatory marker elevation, disease activity, and radiographic damage.

2.4 Laboratory Tests

All the patients were assessed by complete blood count (CBC), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

2.5 Statistical Analysis of the Data

Data were analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Qualitative data were described using the number and percentage. Quantitative data were described using the mean and standard error of the mean. The probability value (*p*-value) ≤ 0.05 was considered statistically significant.

3. RESULTS

The clinical characteristics of the patients were demonstrated in Table 1. There was a female predominance in our patients as 126 patients out of 179 were females. The mean age of the first group (anti-CCP negative) was 53.05 years old and the mean age of the second group (anti-CCP positive) was 50.43.

In the first group, the mean score of VAS pain was 53.03, VAS of global 64.6 and that of tenderness score was 40.33 while that of physician 59.6. In the second group, the mean score of VAS pain was 53.86, VAS of global 64.64 and that of tenderness score was 45.7, while that of physician 59.6. No statistically significant association was found between anti-CCP positivity and clinical disease activity.

Table 1. Clinical data in the RA patients of the two studied groups

		ACPA – RA	ACPA + RA	P-value
Clinical	**Age mean (SD)**	53.05(14.45)	50.43(14.21)	0.290
	Female, n (%)	45(78.9%)	81(66.4%)	0.081
	Male, n (%)	12(21.1%)	41(33.6%)	0.113
	VAS tenderness	45.74(30.58	40.33(30.18	0.237
	VAS pain	53.86(28.17)	53.03(28.58	0.903
	VAS global	63.95(23.04)	64.64(25.64	0.575
	VAS physician	59.60(20.622)	59.53(23.76)	0.74
	TJC, n/28	13.09(7.58)	11.25(7.31)	0.164

VAS: Visual Analogue Scale

Table 2. Laboratory and histological data in the RA patients of the two studied groups

		ACPA – RA	ACPA + RA	P-value
laboratory	**ESR mm/h (median (IQ))**	39.81(31.56)	36.82(26.26)	0.93
	CRP mg/dl (median (IQ))	17.45(25.33)	19.2(22.47)	0.52
	RF titre (IU) (median (IQ))	54.5(98.5)	162.7(180.2)	**<0.001****
Synovial tissue	**Synovitis score (median (IQ))**	3 (9)	4 (9)	0.37

CRP: C Reactive Protein, ESR: Erythrocyte Sedimentation Rate

The laboratory and histological data of the patients were demonstrated in Table 2. In the first group, the mean score of rheumatoid factor (RF) was 54.5, CRP was 17.4 and that of ESR was 39.8. In the second group, the mean score of rheumatoid factor (RF) was 162.7, CRP was 19.2 and that of ESR was 36.82. No statistically significant association was found between anti-CCP positivity and laboratory evaluation of the disease activity (CRP and ESR). Regarding the synovium cellular infiltration, there were no significant differences in the synovium infiltration between both study groups.

4. DISCUSSION

Many studies have been conducted on the generation and pathogenesis of ACPAs (anticitrullinated protein antibodies). It is believed that accumulated citrullinated proteins trigger ACPA production, and the type of ACPA produced can vary depending on the antigens and antibody isotypes involved. The pathogenesis of ACPAs can be divided into two stages, with a marked increase in ACPA levels after the second hit. Furthermore, glycosylation of the antibodies can affect their stability and biological activity, thus enhancing the pathogenicity of ACPAs. Additionally, ACPAs are known to have direct or indirect participation in bone damage.

In a histological point of view, previous reports have supported the short-term anti-inflammatory effects, such as inhibition of synovial hyperplasia, reduction of intra-synovial citrullinated protein, and inhibition of growth factor proliferation, in response to glucocorticoids. So, glucocorticoids can provide excellent short-term inflammatory control and analgesic while the literature presents mixed findings regarding the long-term effects of this intervention [17].

In our study, there was no significant difference in clinical assessment of our patients through VAS in both groups. These agreed with Van Oosterhout et al. who found no statistically significant difference in ACPA-positive and ACPA-negative as regard age, sex, and disease duration, and most of the patients were females [18].

Additionally, there was no significant difference in laboratory assessment of our patients through ESR, and CRP subsequently in both groups. Our results are agreed with Burgers et al. found no significant differences in acute phase reactants [19].

In our study of the synovium structure and its infiltration with inflammatory cells, there were no significant differences in the synovium infiltration between both study groups which demonstrated that synovium that was analysed from both study groups. Gomez-Puerta et al. [20] was consistent with our findings of similarity in the cellular infiltrates' levels between ACPA positive and negative RA patients. As systemic and local inflammation was similar in the study groups, these findings support a similar synovial physiopathology.

This suggests that acute joint pain in RA patients with advanced joint deformities can be prevented successfully with early diagnosis and proper early management [19].

To summarize, the importance of pathology in early diagnosis of RA is magnified and its role in proper management needs more studies. The limitation of this study was the short period, no follow-up evaluation and assessment of accuracy.

5. CONCLUSION

No statistically significant differences were found in synovial cell infiltrates according to the serology.

CONSENT

As per international standard and university standard, patient(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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