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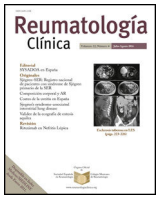

Original article

Ultrasound tenosynovitis: A differential feature of patients with seronegative rheumatoid arthritis

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ABSTRACT

Objective: To identify differential features between patients with seropositive and seronegative rheumatoid arthritis (RA).
Method: Prospective cohort study, including patients who were admitted for polyarthralgia. At baseline was performed: laboratory studies, X-rays of hands and feet, ultrasound of both hands with power Doppler technique, clinical data and clinimetry. In subsequent visits the definitive diagnosis of RA was established or not. It was considered as seronegative RA when patients were negative for both RF and ACPAs.
Results: 746 patients were included, of which 128 (17.1%) ended with a final diagnosis of RA. Of these 128 patients, 87 (67.9%) were seropositive RA, while 41 (32%) were seronegative RA.
The only feature that showed significant differences was the presence of tenosynovitis detected by ultrasound with a positive power Doppler signal, 13.7% of the patients with seropositive RA vs 41.6% of the patients with seronegative RA ($p = 0.0028$).
Conclusion: The only differential feature of patients with seronegative RA was the higher proportion of tenosynovitis detected by ultrasound.

Tenosinovitis ecográfica: una característica diferencial de pacientes con artritis reumatoide seronegativa

Palabras clave:
Artritis reumatoide
Factor reumatoide
Anticuerpos antipéptido cíclico citrulinado
Ecografía
Ultrasonografía
Radiografía

RESUMEN

Objetivo: Identificar características diferenciales entre pacientes con artritis reumatoide (AR) seropositivos y seronegativos.
Método: Estudio de cohorte prospectivo, incluyendo pacientes con poliartralgias. Al inicio se realizó: estudios de laboratorio, radiografías de manos y pies, ecografía de ambas manos con técnica power doppler, datos clínicos y clinimetría. En visitas posteriores se estableció o no el diagnóstico definitivo de AR. Se consideró AR seronegativa cuando los pacientes eran negativos tanto para factor reumatoide como para anticuerpos antipéptido cíclico citrulinado.
Resultados: Se incluyeron 746 pacientes, de los cuales 128 (17,1%) terminaron con diagnóstico final de AR. De estos 128 pacientes, 87 (67,9%) eran AR seropositivos, mientras que 41 (32%) eran AR seronegativos.
La única característica que mostró diferencias significativas fue la presencia de tenosinovitis detectada por ecografía con señal power doppler positiva, el 13,7% de los pacientes con AR seropositiva frente al 41,6% de los pacientes con AR seronegativa (p = 0,0028).

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Conclusión: El único rasgo diferencial de los pacientes con AR seronegativa fue la mayor proporción de tenosinovitis detectadas por ecografía.

Introduction

Rheumatoid arthritis (RA) is one of the most prevalent chronic inflammatory diseases with an incidence of 0.5–1%.[1]

The identification of rheumatoid factor (RF) and anticitrullinated protein antibodies (ACPAs) has led to the recognition of the subgroups of seropositive and seronegative RA.[2]

RF and ACPAs have been regarded as poor prognostic markers of RA and are used as evidence to justify intensive treatment in seropositive RA patients.[3] However, it is uncertain whether patients with seropositive RA manifest worse clinical presentation and disease course compared with seronegative RA patients in disease activity measures other than radiologic outcome and studies remain conflicting.[2,4–7]

The aim of the present study was to estimate the frequency of RA in a cohort of patients who consulted for polyarthralgia, including arthralgia of the hands, and to identify differential features between patients with seropositive RA and seronegative RA.

Methods

A prospective longitudinal study including consecutive patients older than 18 years who were admitted for polyarthralgia (joint pain), including arthralgia of the hands, to "Reuma-check" ® program[8] was performed from August 2017 to March 2020. This program includes at baseline: clinical assessment, laboratory tests, ultrasound (US) with power Doppler (PD) of both hands and radiography (X-ray) of both hands and feet. Each one of the evaluators (laboratory, images and clinician) was blinded to the data of the other studies.

Baseline clinical assessment

All necessary information to complete Clinical Disease Activity Index (CDAI)[9] and Disease Activity Index in 28 joints-erythrocyte sedimentation rate (DAS28-ESR)[10] was collected. Demographic characteristics, including age and gender were assessed. Musculoskeletal assessment was performed according to standard clinical procedures and included: Tender Joint Count (TJC 28), Swollen Joint Count (SJC 28), visual analogue scale with respect to patient global perception of disease activity (VAS patient global) and visual analogue scale with respect to physician global perception of disease activity (VAS physician global). Function was assessed by the Argentinean version of Health Assessment Questionnaire-Disability Index (HAQ-DI).[11]

Baseline laboratory tests

Erythrosedimentation rate (ESR), C-reactive protein (CRP), RF (immunoturbidimetry) and ACPAs (chemiluminescence) were determined in all patients on the same day of the clinical assessment.

Baseline ultrasound evaluation

All US examinations were performed by the same rheumatologist with extensive experience on this imaging technique, on the same day of the clinical assessment. Patients were asked not to talk with the operator during the US examination. A MyLab 25 Gold (Esaote) machine with a multifrequency linear transducer (6–18 MHz) was used. A standardized scanning method recommended by EULAR[12] was used. The following joints were bilaterally: wrist, 2nd to 5th metacarpophalangeals and 2nd to 5th proximal interphalangeals, giving a total of 22 assessed joints per patient. Joint cavity widening, due to the presence of synovial fluid and/or synovial hypertrophy (grayscale synovitis) according to the OMERACT ("Outcomes measures in Rheumatology") preliminary definitions[13], was evaluated at each joint. All joints were evaluated with PD technique to assess the presence of increased abnormal synovial vascularization. Intraarticular PD signal was scored on a semiquantitative scale from 0 to 3 (Grade 0 = no intraarticular PD signal; Grade 1 = presence of a single PD signal; Grade 2 = more than two confluent foci of PD signal but occupying less than 50% of intraarticular area; Grade 3 = PD signal in more than 50% of the intraarticular area). Twenty tendons per patient were assessed: 6 carpal extensor compartments and flexor tendons of 2nd to 5th fingers bilaterally. Tenosynovitis was defined according to the OMERACT preliminary definitions as hypoechoic or anechoic thickened tissue with or without fluid within the tendon sheath, which is seen in 2 perpendicular planes, and which may exhibit Doppler signal. At tendon level PD signal was considered as present or absent.

In order to maximize PD sensitivity and trying to avoid the presence of artifacts, the settings of PD were adjusted as follow: low pulse frequency repetition (PRF) (between 500 and 1000 Hz), dynamic range 20–40 dB, low wall filters (2–3) and PD gain below the level at which color noise appeared in the underlying bone.

Baseline radiography assessment

X-ray of hands and feet were performed on the same day of the clinical assessment. The presence or absence of bone erosions was determined by an experienced rheumatologist, at any joint included on the Sharp/van der Heijde scoring method.[14]

Follow-up

All patients were followed-up after baseline evaluation by their treating rheumatologists and a definitive diagnosis of RA according to the ACR/EULAR 2010 criteria[15] was established or not. It was considered as seronegative RA when the patients were negative for both RF and ACPAs. Patients with personal or family history of psoriasis were excluded. Also were excluded all patients who had any other feature associated with spondylarthritis by the interview.

The study was conducted according to the Declaration of Helsinki and local regulations. Ethical approval for the study was obtained from the Hospital's local ethics committee and informed consent was obtained from all patients.

Statistical analysis

Descriptive statistic was used to summarize patients' characteristics. Continuous variables were expressed as medians and interquartile range (IQR) or as means and standard deviation (SD), and categorical variables were expressed as percentages with their corresponding 95% confidence intervals (95%CI). Comparisons were

Table 1
Characteristics of patients with a final diagnosis of rheumatoid arthritis.

	Rheumatoid arthritis, *n*: 128
Age (years), mean (SD)	56.6 (14.2)
Female, *n* (%)	90 (70.3)
Time between the onset of symptoms and the baseline visit (months), median (IQR)	12 (5–36)
Time between baseline assessment (clinical presentation) and diagnosis of RA (weeks), median (IQR)	2 (2–2)
Smoking, *n* (%)	54 (42.1)
Patient global VAS (0–100), mean (SD)	55.7 (18.1)
Tender joints (28), mean (SD)	5.3 (3.2)
Swollen joints (28), mean (SD)	1.9 (2.7)
CDAI, mean (SD)	17.7 (8)
DAS28-ERS, mean (SD)	4.2 (1.1)
HAQ-DI, mean (SD)	0.8 (0.4)
RF, *n* (%)	83 (64.8)
ACPAs, *n* (%)	51 (39.8)
ESR, mean (SD)	29.8 (24.7)
CRP, mean (SD)	9.7 (19.8)
X-ray bone erosions, n (%)	23 (17.9)
Ultrasound tenosynovitis with positive power Doppler signal, *n* (%)	21 (16.4)
Ultrasound synovitis with positive power Doppler signal, *n* (%)	37 (28.9)

SD: standard deviation; IQR: interquartile range; VAS: visual analogue scale; CDAI: Clinical Disease Activity Index; DAS28-ERS: Disease Activity Index in 28 joints-erythrocyte sedimentation rate; HAQ-DI: Health Assessment Questionnaire-Disability Index; RF: rheumatoid factor; ACPAs: anticitrullinated protein antibodies; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; X-ray: radiography.

performed using parametric and non-parametric tests for continuous variables and the chi-squared test for categorical variables.

Results

A total of 746 (74.4% female and mean age 53.6 years, SD: 14.5) patients with polyarthralgia, including hand arthralgias, were included, of which 128 (17.1%, 95% CI: 14.6–20) ended with a final diagnosis of RA (Table 1). Of these 128 patients, 87 (67.9%) were seropositive (RF and/or ACPAs positive), while 41 (32%) were seronegative (RF and ACPAs negative).

Table 2 shows a comparison of the different features between patients with seropositive RA and seronegative RA. The only feature that showed significant differences was the presence of tenosynovitis detected by US with a positive PD signal, 13.7% of the patients with seropositive RA vs 41.6% of the patients with seronegative RA ($p = 0.0028$).

Tenosynovitis detected by US with a positive PD signal was found in 74 out of 2560 (2.9%) assessed tendons. The most frequent tendons with tenosynovitis by US were 4th and 6th carpal extensor compartments and 2nd and 3rd flexor tendons (27%, 21.6%, 22.9% and 20.2% respectively).

Discussion

The frequency of RA in our cohort of patients with polyarthralgia, including arthralgia of the hands, was 17.1% (128/746), being 67.9% (87/128) seropositive RA and 32% (41/128) seronegative RA, respectively.

Unlike previous studies that showed disparate results regarding differences in inflammatory status, functional ability and radiological data between seropositive and seronegative RA patients,[2,4–7] we did not find differences at the time of clinical presentation between these subgroups of patients regarding clinical inflammatory involvement, acute phase reactants, functional ability and X-ray bone erosions. Furthermore, we did not find differences in joint inflammatory involvement detected by US with power Doppler technique at hands level. However, tendon inflammatory involvement detected by US with PD technique was greater in the subgroup of patients with seronegative RA (41.6%) compared to patients with seropositive RA (13.7%), and this was the only significant difference ($p = 0.0028$) that we found at the time of clinical presentation among these subgroups of patients.

In agreement with our study, Nordberg L.B. et al. also found a higher proportion of tenosynovitis detected by US in patients with seronegative RA compared to patients with seropositive RA, but unlike our study they also found a higher proportion of synovitis detected by US in the subgroup of patients with seronegative RA.[2] This could reflect the differences in both the type and number of joints evaluated in the two studies, we evaluated by US 20 joints of the hands while they evaluated 36 joints of the hands, elbows and lower limbs.

Considering the results of our study, we can affirm that patients with seronegative RA presented practically the same as patients with seropositive RA, even with a greater inflammatory involvement at tendon level detected by US. Therefore, when monitoring and making therapeutic decisions, both subgroups of patients, seronegative and seropositive RA patients, should be treated equally in the first instance. Unfortunately, and as a main limitation of our study, we do not have data from the follow-up of all patients to see their therapeutic outcomes and whether the diagnosis of seronegative RA could have become seropositive RA or in another rheumatological disease. However, the strengths of our study are

Table 2
Comparison of the different features between patients with seropositive and seronegative rheumatoid arthritis.

	Seropositive rheumatoid arthritis, *n*: 87	Seronegative rheumatoid arthritis, *n*: 41	*p* value
Age (years), mean (SD)	56.4 (13.7)	57 (15.5)	0.84
Female, (%)	70.1	70.7	0.94
Smoking, (%)	54.4	44	0.36
Patient global VAS (0-100), mean (SD)	54.9 (17.4)	58.7 (21.2)	0.54
Tender joints (28), mean (SD)	5 (3.3)	6.3 (2.9)	0.08
Swollen joints (28), mean (SD)	1.9 (2.9)	2.2 (2.1)	0.65
CDAI, mean (SD)	17.1 (8.3)	19.7 (6.8)	0.16
DAS28-ERS, mean (SD)	4.1 (1.1)	4.5 (1.1)	0.16
HAQ-DI, mean (SD)	0.8 (0.4)	0.9 (0.4)	0.23
ESR, mean (SD)	30.8 (25)	26.3 (23.6)	0.41
CRP, mean SD)	9.9 (21)	8.9 (15.5)	0.81
X-ray bone erosions, (%)	22.7	20	0.77
Ultrasound tenosynovitis with positive power Doppler signal, (%)	13.7	41.6	0.0028
Ultrasound synovitis with positive power Doppler signal, (%)	34.9	32	0.78

SD: standard deviation; VAS: visual analogue scale; CDAI: Clinical Disease Activity Index; DAS28-ERS: Disease Activity Index in 28 joints-erythrocyte sedimentation rate; HAQ-DI: Health Assessment Questionnaire-Disability Index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; X-ray: radiography.

based on the large cohort of patients included and the detailed baseline study in all these patients, including clinical evaluation, laboratory and imaging techniques, both X-ray and US.

In conclusion, the frequency of RA in our cohort of patients with polyarthralgia, including hand arthralgias, was 17.1% and the only differential feature of patients with seronegative RA was the higher proportion of tenosynovitis detected by US with a positive PD signal in comparison with patients with seropositive RA.

Author's contribution

All authors contributed substantially to the conception and design of the work and acquisition and interpretation of the data. SR and RGS additionally analyzed the data and drafted the initial version of the manuscript. The final manuscript has been revised critically and approved by all the authors and they have given the necessary attention to ensure the integrity of the work.

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Conflict of interest

All authors declare they have no conflict of interest regarding the present study.

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