Epidemiological profile of patients with extra-articular manifestations of rheumatoid arthritis from the city of Curitiba, South of Brazil

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ABSTRACT

Objectives: To describe the epidemiological profile of patients with extra-articular manifestations of rheumatoid arthritis (ExRA) from an university-affiliated rheumatology center; to report the prevalence of ExRA and to compare it with available data; and to identify, if possible, ExRA predictors. **Methods:** This study reviewed 262 medical charts of patients previously diagnosed with rheumatoid arthritis (RA) according to the 1987 American College of Rheumatology criteria, and attending that rheumatology center in 2010. The statistical analysis comprised simple mathematical calculations, Student *t* and chi-square tests, and a significance level of 5% ($\alpha = 0.05$). **Results:** During the course of the disease, 120 patients (45.8%) had ExRA. Pulmonary manifestation, rheumatoid nodules and Sjögren's syndrome were the most common manifestations found. Rheumatoid factor and anti-cyclic citrullinated peptide antibody were positive in most patients tested. Most patients were classified as Steinbrocker functional classes 1 and 2. The mean DAS-28 was 3.629, and the mean HAQ score, 1.12. Patients with ExRA had longer disease duration ($P < 0.05$), and current smoking habit associated with the presence of ExRA ($P < 0.05$). **Conclusions:** The prevalence of ExRA during disease course was 45.8%, and current smoking habit correlated with the presence of ExRA.

Keywords: rheumatoid arthritis, health profile, smoking.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic and multisystemic disease of unknown etiology, characterized by inflammatory synovitis. It is a symmetric and additive polyarthritis with a variable potential for deformation, usually involving peripheral joints and the spine. It affects 1% of the general population, being three times more frequent in women than men. Its prevalence increases with age, and the difference between the genders becomes smaller. It usually begins between 35 and 50 years of age, and its onset relates to genetic predisposition and to the interaction of environmental agents with that predisposition.[1]

The inflammatory process can spread to other systems and organs, causing extra-articular manifestations of RA (ExRAs), which can affect equally men and women, and can appear at any age.[2] Forty percent of the patients are estimated to have ExRAs during the course of disease, 15% being considered severe.[3]

Some predictors of ExRAs are as follows: male gender; severe joint disease; low functional capacity; high levels of inflammatory markers; and high titers of autoantibodies, such as rheumatoid factor (RF), anti-cyclic citrullinated peptide antibody (anti-CCP), and antinuclear antibody (ANA). Both RF and anti-CCP are also related to the severity of ExRA.[2,4,5] Smoking, longer duration of disease, and RA associated with the HLA-DRB1*04 genes are also predictors of ExRAs. Probably due to interactions between those and other risk factors, more than one ExRA tend to occur in the same patient.

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Rheumatoid nodules are associated with a large spectrum of severe ExRA.[2,6]

There are several definitions for ExRAs depending on the clinical and/or pathological criteria used. The lack of an international consensus and of a single classification is partially due to differences observed in rheumatology texts, case reports, and incidence studies. Other reasons are discrepancies in the definition of cases and variations in the inclusion of manifestations other than the classic ExRAs. Some non-articular findings have been classified as complications of RA rather than ExRAs, while others, which have been described as neither ExRAs nor complications, have been included due to their increased risk of RA.[7] This limits comparisons between different studies.

Recent publications have suggested that the use of a similar criterion would enable a more consistent assessment of the extension of the extra-articular disease. Turesson et al.[8] have proposed a set of criteria for severe ExRAs, developed to identify clinically important ExRAs in retrospective structured studies reviewing medical charts.

Some examples of ExRAs commonly found in the literature are as follows: rheumatoid nodules; pericarditis; pericardial effusion; pleuritis; pleural effusion; interstitial pulmonary disease; pulmonary artery hypertension; Caplan's syndrome; Felty's syndrome; chronic disease anemia; thrombocytosis; neuropathy; scleritis; episcleritis; sicca syndrome; scleromalacia perforans; glomerulonephritis; cutaneous ulcers; vasculitides; De Quervain's tenosynovitis; amyloidosis; and Sjögren's syndrome.[4–6,8,9]

The systemic inflammatory process is the major predictor of mortality for patients with RA. The presence of ExRAs determines a five-fold increase in mortality rate as compared with that of patients without ExRAs, and that increase is even greater when co-morbidities, such as cardiovascular and pulmonary diseases, malignancies and dementia, are considered. Some ExRAs, especially vasculitis, pericarditis, pleuritis, amyloidosis and Felty's syndrome, are associated with a shorter life expectancy as compared with that of patients without ExRAs. There is also a particularly increased risk of premature death due to cardiovascular disease. The survival of patients with RA but no ExRA is similar to that of the general population.[2,3,8,10–12]

Considering the patients with ExRAs from a referral service, this study aimed at the following: describing their epidemiological profile; reporting the prevalence of ExRAs among them; comparing their ExRAs with data in the literature; and, if possible, identifying predictive factors of those manifestations.

PATIENTS AND METHODS

This is a retrospective study based on data obtained from the medical charts of patients with RA from the Service of Rheumatology of the Hospital Universitário Evangélico de Curitiba (HUEC).

This study included patients diagnosed with RA according to the 1987 American College of Rheumatology (ACR) classification criteria for RA, and who attended the service of rheumatology of the HUEC from January to December 2010.

The following patients' data were collected: gender; age; city of residence; ethnicity; educational level; current and previous smoking habit; duration of smoking habit; age at diagnosis; disease duration; co-morbidities; presence of ExRA during the course of disease; autoantibodies (RF, ANA, anti-CCP, anti-Ro and anti-La); global functional class by use of the Steinbrocker functional classification and the Health Assessment Questionnaire (HAQ); and parameters of disease activity by use of the Disease Activity Score 28 (DAS-28). The latter two corresponded to the last consultation of the year.

Ethnicity was stratified according to the traditional records of the service as follows: Caucasian; mixed heritage; black; Asian; and Brazilian native. The educational level was classified according to the records of the service as follows: illiteracy/incomplete elementary education; complete elementary education; incomplete secondary education; complete secondary education; incomplete higher education; and complete higher education. The concomitant conditions not described in the literature as direct consequences of RA, even though some of them are more frequently associated with RA, were considered co-morbidities

The ExRAs were grouped according to affected systems or organs as follows: rheumatoid nodules; rheumatoid vasculitis; lymphadenopathy; amyloidosis; Sjögren's syndrome; and hematological, pulmonary, cardiac, ocular, neurological, renal, and osteomuscular manifestations. Because of the lack of a consensus in the current literature regarding the classification of ExRAs, our findings were described based on an adaptation of the descriptions found in books and reference articles, such as the articles by Turesson et al.[6,8] and the book *Rheumatology*.[2]

Regarding autoantibodies, ANA was assessed by use of indirect immunofluorescence. The results were standardized according to the II Brazilian Consensus on ANA Hep-2, and were positive when titers were > 1:80, according to the laboratory of the HUEC. Rheumatoid factor (IgM) was obtained by use of the qualitative latex agglutination test, and measurements > 20 UI/mL were considered positive. Anti-CCP (IgG) was determined by use of the Enzyme-Linked Immunosorbent

Assay (ELISA), with a cutoff point of 20 U/mL. Titers between 20 and 39 U/mL were considered weakly positive; between 40 and 59 U/mL, moderately positive; and over 60 U/mL, strongly positive. The anti-Ro and anti-La autoantibodies were tested by use of ELISA.

The Steinbrocker functional classification comprises four classes, according to the individual's capacity of performing daily life tasks. Class 1 corresponds to complete functional capacity with ability to carry on all usual duties without handicaps; class 2, functional capacity adequate to conduct normal activities despite handicap of discomfort or limited mobility in one or more joints; class 3, functional capacity adequate to perform only few or none of the duties of usual occupation or of self-care; class 4, largely or wholly incapacitated (patient bedridden or confined to wheelchair).[1]

The HAQ involves questions related to daily life, regarding eight predetermined groups, the result being divided by eight. The final score represents the individual's quality of life. The higher the score, the worse the quality of life.[13] The DAS-28 assesses RA activity by use of a mathematical equation that comprises the following: Visual Analogue Scale for pain score (ranges from zero to ten, where zero means no pain, and ten means worst pain imaginable); tender joint count; swollen joint count; and erythrocyte sedimentation rate (mm/h). Results over 5.1 indicate high disease activity; 3.2–5.1, moderate activity; 2.6–3.2, low activity; and under 2.6, remission.[13]

This study included 262 medical charts according to pre-established criteria. Data were inserted into Excel 2007 (Microsoft) sheets and managed to provide the epidemiological profile through descriptions and simple mathematical calculations, such as percentage and arithmetic mean.

To assess whether disease duration differed between patients with and without ExARs, Student *t* test was used (ZAR 1999). The chi-square test was used to assess the differences between the proportions of patients with or without ExARs regarding several variables, such as ethnicity, current smoking habit, previous smoking habit, RF, anti-CCP, and gender.

There was only one individual of Native Brazilian origin, a fact that made it impossible to assess him statistically; therefore, he was excluded from the analysis regarding ethnicity. For all analyses, a significance level of 5% was adopted ($\alpha = 0.05$). The statistical analyses were performed using the Statistica (Statsoft) statistical package and the tables developed with Excel 2007 (Microsoft).

This study was approved by the Committee on Ethics and Research of the Sociedade Evangélica Beneficente de Curitiba (protocol # 12103/10, December 2010) and has no conflict of interest.

RESULTS

During the course of disease, 120 patients had ExRA, corresponding to 45.8% of the patients with RA in the period studied, and most of them were of the female gender (84.1%). The mean age was 56 years (range, 29–87 years; mode, 61 years). The cities of residence were obtained from 101 patients and were as follow: Curitiba, 64; São José dos Pinhais, 4; Ponta Grossa, 2; Pinhais, 2; Colombo, 2; Campo Largo, 2; Paranaguá, 2; Araucária, 2; and other cities in the state of Paraná, 21. Regarding ethnicity, 71 patients (71.7%) were Caucasian, 23 (23.2%) were of mixed heritage, five (5%) were black, and 21 had no ethnic records. Mean age at diagnosis was 44 years (range, 11–83 years; mode, 50 years). Mean duration of disease was 12.2 years (range, 0–64 years). Data on education level were found in 80 medical charts and are shown in Table 1.

Regarding smoking habit, only one medical chart showed no smoking record. Of the others, 82 patients (69%) were not current smokers, and 23.5% of the total number of patients were previous smokers, with a mean duration of tobacco use of 20.2 years – eight patients were excluded from that calculation due to lack of information. Thirty-seven individuals (31%) were current smokers, with a mean duration of tobacco use of 26 years.

The patients' major co-morbidities during the study period are shown in Figure 1. Many of them, such as systemic arterial hypertension (SAH), dyslipidemia, and hypothyroidism, were found concomitantly in the same patient. The specifications of the most common ExRA types, according to affected organs or systems, are shown in Table 2.

Regarding autoantibodies, RF was positive in 83 patients (69.2%), and ANA was positive in 32 (27.1%) of the 118 medical charts providing this information, most showing high titers (> 1:160). Of the 62 patients with data on the anti-CCP serological test, 48 (77%) were positive. Of the 114 patients with data on the anti-Ro test, only six (5.3%) were positive. Of the 115 patients with data on the anti-La test, three (2.6%) were positive.

Table 1
Educational level, %* (n)

Illiteracy/ incomplete Elementary Education	62.5 (50)
Complete Elementary Education	13.75 (11)
Incomplete Secondary Education	2.5 (2)
Complete Secondary Education	16.25 (13)
Incomplete Higher Education	0
Complete Higher Education	5 (4)

*Total corresponds to 80 individuals whose data were available

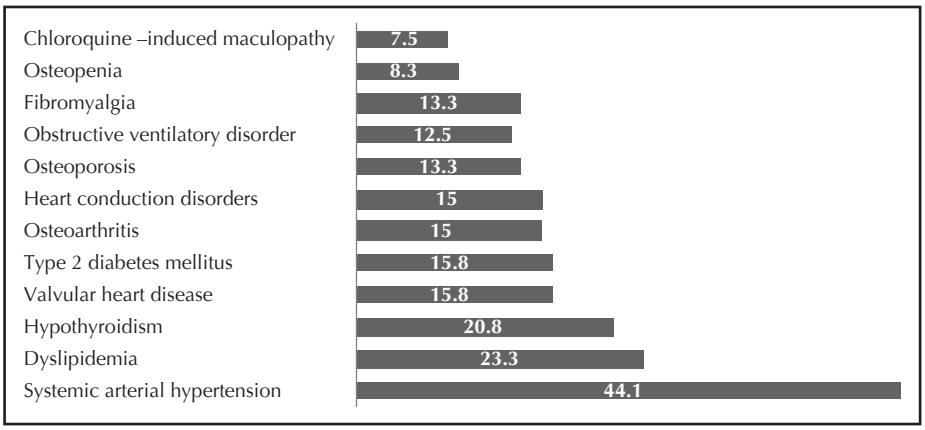

Figure 1
Co-morbidities of patients with extra-articular manifestations of rheumatoid arthritis (%).

Table 2
Most common types of extra-articular manifestations of rheumatoid arthritis, %*(n)

Rheumatoid nodules	21 (25)	—
Hematological	4.2 (5)	Chronic disease anemia
Pulmonary	54.2 (65)	Pulmonary fibrosis Pulmonary nodules Pleural effusion Pulmonary artery hypertension
Cardiac	1.7 (2)	Pericardial effusion Pericarditis
Ocular	3.4 (4)	Episcleritis Scleritis Scleromalacia perforans
Neurological	3.4 (4)	Polyneuropathy Peripheral mononeuropathy
Renal	0	—
Vasculitides	10 (12)	Raynaud Ulcer Others
Osteomuscular	1.7 (2)	De Quervain's tenosynovitis
Amyloidosis	12.5 (15)	—
Sjögren's syndrome	18.3 (22)	—

*Regarding the total number of patients. Many of them had more than one ExRA.

Considering functional assessment (Steinbrocker functional classification), four medical charts showed none. One hundred patients (86%) provided answers compatible with classes 1 and 2, and 16 (14%) with classes 3 and 4. The mean value of DAS-28 for 108 patients who provided that information in 2010 was 3.629 (range, 1.19–7.45). The HAQ score in 2010 was found in 50 medical charts, its mean value being 1.12 (range, 0–2.8).

The analyses showed that patients with ExRA had longer disease duration than those with no ExRA (Table 3). The proportions assessed allowed stating that there is difference only between the proportions of currently smokers with ExRA. Smoking habit is associated with the presence of ExRA (Table 4).

Table 3
Means, standard deviations (SD), sample size (n) and probability (P) associated with the Student *t* test

Presence of extra-articular manifestations	n	Mean	SD	P
Yes	120	12.3	9.6	0.002*
No	141	8.9	7.4	0.002*

*P < 0.05.

Table 4
Proportions (data as absolute frequencies) of six distinct variables associated with the presence or absence of extra-articular manifestations

Variable (n)		Presence of ExRA		P
		Yes	No	
Gender (n = 262)	Female	101	126	0.279
	Male	19	16	
Ethnicity (n = 216)	Caucasian	71	89	0.244
	Mixed heritage	23	18	
	Black	5	10	
Current smoking (n =260)	No	82	113	0.037*
	Yes	37	28	
Previous smoking (n = 192)	No	53	77	0.564
	Yes	28	34	
RF (n = 262)	No	36	54	0.172
	Yes	84	88	
Anti-CCP (n = 111)	No	13	15	0.2453
	Yes	49	34	

*P < 0.05. ExRA: extra-articular manifestations of RA; RF: rheumatoid factor.
P values are associated with the chi-square test.

DISCUSSION

The prevalence of ExRA found in this study (45.8%) was similar to that found in a prospective cohort study with a 46-year follow-up carried out in Minnesota, USA, which reported a 30-year cumulative incidence of 46%,[8] and to another found in a retrospective study carried out in Turkey, which assessed 526 medical charts in 2006 and reported a 38.4% frequency of ExRA.[14] It differs, however, from other publications. A retrospective study carried out in the state of São Paulo has found a 23.3% prevalence of ExRA in three years,[15] and a one-year follow-up carried out in France in 82 centers has reported an ExRA prevalence of 8.4%.[16] Such differences are due to the heterogeneity of the classifications used by each author.

The epidemiological profile of the patients with ExRA in our study differed from that found in the study carried out in the state of São Paulo, which also comprised patients from the Brazilian Unified Health Care System.[15] The mean disease duration was an exception, considering that in the study carried out in the state of São Paulo it was 7.2 years.

Regarding co-morbidities, SAH was found in 44.1% of the patients with ExRA, which is higher than the 30% of the general population.[17] A Colombian study of 2009 showed prevalences of 22% and 13% in patients with RA and with and without ExRA, respectively.[10]

Type 2 diabetes mellitus was described in 15.8% of the patients with ExRA, a value similar to that of the general population (7.6%; range, 5%–10%).[18] That co-morbidity has not been more frequently reported in patients with ExRA or only RA.

Rheumatoid arthritis *per se* is known to increase the chance of cardiovascular diseases and acute ischemic events.[10] In addition, severe extra-articular disease predisposes to the occurrence of an earlier first cardiovascular event. The incidence of acute myocardial infarction can increase up to four times.[19,20] Although some patients die due to specific complications of RA, such as cervical instability or side effects from drugs, most mortality is due to other associated diseases, particularly cardiovascular disease.[21]

Hypothyroidism was identified in 20.8% of the patients, a prevalence higher than the 1% reported for the general population, and 5% for those over the age of 60 years.[22] Dyslipidemia was found in 23.3% of the patients, below the value expected for the general population (38% for the male gender, and 40% for the female gender).[23]

Approximately 30.8% of the sample studied had valvular heart disease or heart conduction disorder. Some authors consider those changes part of the ExRAs.[9] A methodology that better specifies electrocardiographic findings and considers the differential diagnosis with the side effects of drugs used to treat RA, such as antimalarials, would be necessary.[1] The general consensus, however, is not to include that type of heart involvement in the ExRA group.[8]

Osteoarthritis (OA) was present in 15% of the patients studied and was part of the differential diagnosis of RA. The prevalence of the symptomatic hand OA defined by the ACR varies from 2% in European population studies to 8% in North-American studies and 14.9% in studies with an Italian population.[24] A 2010 study showed that the mean age of patients with OA coincides with the mean age of patients with ExRA.[25]

Together, osteoporosis and osteopenia were comorbidities present in 21.8% of the patients. Osteoporosis is a significant clinical problem in RA. Patients not only have osteopenia and juxta-articular erosion, but also osteoporosis at sites away from the inflamed joints. The pathogenesis is multifactorial and disease activity is the major determinant of bone mass loss, in addition to treatment with glucocorticoids, reduced mobility, and estrogen and/or androgen deficiency.[26] Osteoporosis was diagnosed by use of bone densitometry, Hologic dual-energy X-ray absorptiometry (DXA), assessing anteroposterior regions of lumbar spine and right femur, and the results were classified according to the World Health Organization criteria (osteopenia, T score: −1.0 to −2.4; osteoporosis, T score ≤ −2.5).

On spirometry, a 12.5% prevalence of obstructive ventilatory disorders was found. That test is routinely performed in all patients with RA at the Rheumatology Service of the HUEC, and obstructive ventilatory disorders are frequently found in the general population. Fibromyalgia was identified in 13.3% of the patients studied, being considered a differential diagnosis of RA.[27] Its prevalence in the general population is approximately 2%, and it can be found in 25% of the patients with RA. This has implications for the treatment and impacts the quality of life assessments and the appearance of psychiatric disorders, such as depression.[28]

The prevalence of chloroquine-induced maculopathy was 7.5%. That antimalarial drug is known to cause keratopathy and retinopathy as side effects, the event being related to the drug dose and duration of its use. Hydroxychloroquine is known to have a decreased effect. Careful ophthalmologic follow-up of patients on that drug should be performed.[1,29,30]

Pulmonary manifestations were the most frequent ExRAs found (54.2%), and that frequency was greater than that reported in other studies (10%–20%). A study carried out in São Paulo has reported a 15% frequency.[15] Pulmonary manifestations are believed to appear within the first five years after

the diagnosis of RA. Although pulmonary infections and/or pulmonary toxicity due to drugs are frequent complications, pulmonary disease directly associated with RA is more common. Although cardiovascular diseases are responsible for most deaths related to RA, pulmonary complications are common and directly responsible for 10%–20% of the deaths directly attributed to RA.[31]

Rheumatoid nodules were found in 21% of the patients studied, as compared with literature reports of 20%–35%. Those values coincide with that reported in the study carried out in São Paulo[15] (29%) and that by Turesson et al.[6] (34%). Rheumatoid nodules correlate with the appearance of ExRA and with a poor prognosis of RA in general.[1,15,32]

Concomitance of secondary Sjögren's syndrome was found in 18.3% of the sample studied. A study at the same service carried out in 2007 reported a 12.1% concomitance of that syndrome.[33] The study carried out in São Paulo has reported concomitance of that syndrome in 28% of the sample,[15] while Turesson et al.[6] have reported it in 11.4% of their sample. It is the most common ocular manifestation. Secondary Sjögren's syndrome is diagnosed at the rheumatology service of the HUEC according to the European criteria modified by the American-European Consensus Group for Sjögren's syndrome in 2002.[34] Other ocular manifestations, such as episcleritis, scleritis, and scleromalacia perforans, were less frequently reported (4.2%).

Secondary amyloidosis was found in 12.5% of the patients. Al-Ghamdi et al.[32] and Turesson et al.[6] have reported 6% and 0.7%, respectively, in their studies, while Çalgüneri et al.,[14] 1.1% of the patients. That ExRA is considered rare and usually develops in patients with long-term RA, worsening their prognosis.[29] At the rheumatology service of the HUEC, that manifestation is screened in patients with disease for more than five years, by use of abdominal fat biopsy and hematoxylin-eosin (HE) staining, regardless of the presence of symptoms.

Vasculitides, such as Raynaud's phenomenon and ulcers, had been reported by 10% of the patients, a value slightly over that reported by Turesson et al.[35] (3.6%) and Çalgüneri et al.[14] (1.3%). Rheumatoid vasculitis typically affects small and medium vessels, being associated with high rates of early mortality, with approximately 40% of the patients dying in five years. It also has significant morbidity, because of organ damage caused by vasculitis and consequent to treatment.

Approximately 4% of the sample had hematological manifestations during the course of disease. Anemia caused by chronic disease was the most common finding in our group, in accordance with data in the literature (60% of hematological manifestations).[29] Al-Ghamdi et al.[32] have reported 8.2%.

Neurological ExRAs were found in 3.4% of the patients. In the literature, that value varies from 0.5% to 80%.[36] Clinically detectable involvement of the peripheral nervous system in RA is uncommon. It can be asymptomatic at initial stages or have a large variety of symptoms, such as pain, paresthesia, and muscle weakness.

Cardiac involvement was identified in 2.5% of the sample. A French study has reported pericarditis as the major ExRA, and it correlated with poor prognosis.[8,16] Systemic inflammation in RA can lead to cardiac involvement, pericarditis being the most common, through mechanisms of vasculitis, nodule formation, amyloidosis, serositis, valvulitis, and fibrosis.[29]

De Quervain's tenosynovitis was found in 1.7% of the patients. One study on hand involvement of patients with RA has reported a 33% frequency of De Quervain's tenosynovitis.[37] De Quervain's tenosynovitis is known, similarly to synovitis (and can have its effects added), to cause joint destruction and instability and muscle function unbalance. There are not many studies relating predictors to that type of manifestation. One study has reported the difficulty in using the hands in the first two years of disease as a strong predictor, in addition to the DAS-28 score.[37]

Regarding renal involvement, glomerulonephrites were not reported in our sample. Some patients with chronic renal failure were found; however, due to the existence of co-morbidities, such as SAH and type 2 DM, and to the lack of biopsy to confirm the rheumatoid origin of renal failure, they were not counted as ExRAs.

Positivity for the RF was identified in 69.2% of the patients with ExRAs, similarly to that reported in a study carried out in São Paulo and in a Greek retrospective study (68.2% and 69.5%, respectively).[15,38] The association of RF and extra-articular disease in RA is well known – the RF is considered a predictor of ExRA. The influence of each isotype in that association has been the object of recent studies. One study published in 1995 compared the incidence of ExRA with the presence of different RF isotypes (IgA, IgM, and IgG), reporting that 80% of the patients with ExRA were negative for RF IgA, 70% were positive for IgM, and 64% were positive for IgG.[39] Similarly, a Swiss study of 2007 showed that 90% of the patients with ExRA were positive for RF IgM, 95% were positive for IgA, and 86% were positive for IgG.[40] Patients with seronegative RA are believed to have other autoantibody isotypes, predisposing them to systemic disease.[41]

Positivity for ANA was identified in 27.1% of the patients with ExRA tested for ANA, a percentage lower than that reported in other studies. Turesson et al.[40] have found positivity for ANA in 45% of the patients with ExRA, while Al-Ghamdi

et al.[42] have reported 38%. Regarding patients undergoing anti-CCP testing, 77% of them tested positive, in accordance with data in the literature. In 2007, Turesson et al.[5] reported that anti-CCP was positive in 77% of the patients with ExRAs, while a Greek study has reported 65.3% of that association.[38] The presence of anti-CCP in patients with RA indicates more severe joint disease. The presence of citrullinated proteins in inflamed synovia suggests that they play an important role in the pathogenesis of RA. Regarding extra-articular disease, so far we do not know whether those proteins are present in extra-articular sites of RA and whether they can contribute to the local process of disease through an anti-CCP-mediated immune process.[43] The present study found no statistical correlation between anti-CCP and ExRA, probably due to the scarcity of results available. Further studies correlating ExRA and anti-CCP and including serological testing should be performed.

The anti-Ro antibody is associated with several autoimmune diseases, such as Sjögren's syndrome, systemic lupus erythematosus, subacute cutaneous lupus, neonatal lupus, and, less frequently, systemic sclerosis, and RA. The frequency of anti-Ro in RA varies in the literature, and this has been attributed to differences in study methodology and populations. Some studies have reported the association of anti-Ro antibody with manifestations of severe disease, but that observation has not been confirmed in other publications.[44] Usually, 3%–15% of the patients with RA have the anti-Ro antibody,[45] and there are no specific data correlating it with ExRAs. In our study, the association of anti-Ro and ExRAs was observed in 5.3% of the patients. According to the literature, Sjögren's syndrome, peripheral neuropathies, and rheumatoid nodules have been the ExRAs most frequently found in anti-Ro-positive patients.[45]

Regarding the anti-La antibody, few publications have shown its association with RA or ExRAs. It is usually related to lupus and Sjögren's syndrome.

The values found for the Steinbrocker functional classification, DAS-28, and HAQ in our study should be considered as providing an idea of functional capacity, disease activity and quality of life, rather than as reliable data regarding the patients' real conditions. This is because the values obtained during the period studied were single and randomly collected. If the objective was to correlate them with ExRAs, values corresponding to the period the ExRAs appeared should have been obtained. If the objective was to assess data regarding the year 2010, the arithmetic mean of the values obtained throughout that year should have been calculated. Methodological difficulties, in addition to data unavailability in several cases, led the authors to exclude them from this study's analyses.

In this study, the statistical analysis has shown that ExRAs tend to appear in patients with longer disease duration. However, that finding has not been confirmed in the literature, according to which, ExRAs are related to neither disease duration nor its stages.[19]

Current smoking habit was associated with the presence of ExRAs in this study. Al-Ghamdi et al.[32] have not been able to find that association due to the insufficient number of smokers in their sample. Smoking habit, which is a risk factor for RA in general and has been suggested to predict joint damage, has also been reported as a predictor of severe ExRAs.[8] That association has been reported to be independent of RF, indicating the direct or indirect involvement of other pathophysiological mechanisms.[6]

CONCLUSION

The epidemiological profile of patients with RA and ExRAs at the service studied was as follows: 56-year-old Caucasian woman; non-smoker; low educational level; mean age at diagnosis of 44 years; mean disease duration of 12.2 years; and major diseases associated: SAH, dyslipidemia, and hypothyroidism. The prevalence of ExRAs throughout disease course was 45.8%, and a correlation between current smoking habit and appearance of ExRAs was found.

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