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Persistent undifferentiated arthritis: Evaluation of 60 cases

Persistan andiferansiye artrit: 60 olgunun değerlendirilmesi

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Abstract

Objective: Undifferentiated arthritis (UA) is diagnosed after excluding other arthritis-related diseases. Current data generally focuses on the early forms of UA, and knowledge about persistent UA (pUA) is insufficient. Therefore, we investigated the general characteristics of patients with pUA in this study.

Methods: The study included patients with persistent peripheral arthritis of undetermined etiology lasting longer than six months. Medical records were reviewed retrospectively. Patients having an arthritis-associated diagnosis were excluded. Arthritis was verified by magnetic resonance imaging. The disease activity was evaluated with a visual analog scale.

Results: We totally analyzed 60 patients with a mean age of 49.7 years and 76.7% of them were female. The mean disease duration was 78 months, and 21.6% of them had a family history of rheumatic diseases. The most common clinical pattern was knee monoarthritis (56.6%), the number of affected joints was two at most, and the frequency of erosive arthritis was 35%. Among all variables, only metatarsophalangeal joint involvement was significantly higher in patients with erosive arthritis (p=0.046). 98% of patients achieved remission with disease-modifying anti-rheumatic drugs (DMARDs).

Conclusion: Our research shows that pUA shares several characteristics with other rheumatic diseases such as the family history of rheumatic disease, good response to DMARDs, and chronic course. We found that the cases with pUA show mono/oligoarticular involvement as spondyloarthritis; female gender predominance, and (sometimes) erosive course as rheumatoid arthritis. A long lag time is a major problem, and the prognosis of pUA is generally benign. Further studies are needed for a better definition of this clinical entity.

Keywords: Undifferentiated arthritis, persistent arthritis, inflammatory arthritis, chronic arthritis

Öz

Amaç: Andiferansiye artrit (AA), diğer artrit ilişkili hastalıklar dışlandıktan sonra tanısı konulan bir hastalıktır. Literatürdeki çalışmalar genellikle AA'nın erken formu ile ilişkili olup persistan formu için bilgiler sınırlıdır. Bu nedenle çalışmamızda persistan andiferansiye artritli (pAA) hastaların genel karekteristik özelliklerini araştırmayı amaçladık.

Yöntem: Etiyolojisi bilinmeyen ve altı aydan uzun süreli periferik artritli hastalar çalışmaya dahil edildi. Hastaların dosyaları retrospektif olarak incelendi. Artrit ilişkili hastalık tanısı olanlar çalışmadan çıkarıldı. Artrit, manyetik rezonans görüntüleme yöntemi ile doğrulandı. Hastalık aktivitesi vizuel analog skala ile değerlendirildi.

Bulgular: Ortalama yaşı 49,7 yıl olan toplam 60 hasta incelendi ve olguların %76,7'si kadındı. Ortalama hastalık süresi 78 ay olup olguların %21,6'sında romatolojik hastalıklar açısından aile öyküsü mevcuttu. En sık saptanan klinik patern diz monoartritiydi (%56,6), etkilenen eklem sayısı en fazla ikiydi ve hastaların %35'inde eroziv artrit mevcuttu. Tüm değişkenler içinde sadece metatarsofalangeal eklem tutulumu eroziv artritli hastalarda anlamlı olarak daha fazlaydı (p=0,046). Hastaların %98'inde hastalık modifiye edici anti-romatizmal ilaçlar (DMARD) ile remisyon sağlandı.

Sonuç: Araştırmamız pAA'nın romatizmal hastalık açısından pozitif aile öyküsü, DMARD yanıtının iyi olması ve kronik seyir gibi bazı özellikleri diğer romatizmal hastalıklarla paylaştığını göstermektedir. Bununla birlikte pAA'lı olgular spondiloartrit benzeri mono/oligoartiküler tutulum, romatoid artrit benzeri kadın cinsiyet baskınlığı ve (bazen) eroziv seyir göstermektedir. Tanı gecikme süresinin uzun olması önemli bir sorun olup pAA'nın prognozu genellikle iyidir. Bu klinik antitenin daha iyi tanımlanması için ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Andiferansiye artrit, persistan artrit, enflamatuvar artrit, kronik artrit

Introduction

Arthritis is a non-specific physical examination finding of different disease groups such as rheumatologic, malignant, immunological, infection, or systemic inflammatory disorders. Therefore, we should consider many diseases in the differential diagnosis of a patient having arthritis. Arthritis is

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usually attributed to well-defined rheumatic diseases such as rheumatoid arthritis (RA) or spondyloarthritis (SpA) and consulted rheumatologists by physicians. However, many patients with arthritis may not be diagnosed with a specific disease and this clinical situation is known as undifferentiated arthritis (UA). What are the clinical, laboratory, and imaging investigations necessary to define UA, or which differential diagnosis should be excluded? Which patient will develop a persistent UA or erosive UA? The answers to these questions are still uncertain. There is no agree management of UA. Machado et al.[1] published 10 multinational evidence-based recommendations on how to investigate and follow-up UA in 2010. Additionally, some national evidence-based recommendations were published, but there is no accepted consensus/algorithm in general.[2,3]

The early phase of UA is a heterogeneous condition and there are three scenarios for the disease course; progression to a defined disease (7-65%), going under remission (13-60%), or persisting as UA (pUA: 10-40%).[4] If an underlying specific disease is diagnosed, treatment is applied for that, but the management of pUA is unclear. There are numerous guidelines, recommendations, studies, or case reports for specific rheumatological diseases except for pUA, so it is difficult to manage.

In a population-based study, the incidence of pUA was found to be higher that of psoriatic arthritis and ankylosing spondylitis (AS) (respectively 13, 7, and 6/100,000).[5] Also, rheumatologists have not enough data about pUA. In the future, this clinical situation will become a more common problem being faced in daily practice. This study aimed to investigate the general characteristics of patients with pUA. Previous studies are generally about the early phase for UA so our results will be helpful for managing patients with pUA.

Materials and Methods

Patients

We analyzed the patients who were diagnosed with pUA and followed up between August 2018-April 2021 in a secondary central state hospital in the East of Turkey (this study was completed during the period that the author was assigned to that hospital). The patients' electronic files were evaluated retrospectively for clinical, demographic, laboratory, and treatment data; M13.9 was used as an ICD-10 code to define the patients with pUA. The inclusion criteria of patients were; aged 18 years or older, having peripheral arthritis in at least one joint, and the persistence of arthritis for at least six months (we decided on that time span due to two criteria. The first one is early disease-modifying anti-rheumatic drug treatment's effects on radiographic damage. The second criterion is being on the period that the treatment shouldn't be delayed[6]), and not fulfilling any identified classification criteria for a specific disease (such as revised classification criteria for RA[7] and axial or peripheral SpA[8,9]) or during follow-up. Patients were excluded if an arthritis-related disease (rheumatic or non-rheumatic) was detected.

Arthritis was defined as a combination of morning stiffness, pain, and swelling in a peripheral joint; these criteria have 86-90% sensitivity and 90% specificity.[10] Arthritis was confirmed by magnetic resonance imaging (MRI) to exclude intraarticular masses mimicking arthritis, such as pigmented villonodular synovitis and to confirm some cases that didn't have enough clinical evidence for inflammatory arthritis (e.g. absence of joint swelling). The erosive pattern was defined as the eroded bone surface of the area adjacent to the joint by MRI findings. The study was approved by the Ethics Committee of the Mus Alparslan University where the study was conducted.

Assessment and Treatment

At the initial visit, the patient's medical history and physical examination were conducted carefully; symptom duration time, the pattern of joint involvement (number, localization, and distribution of the affected joints), smoking history, and family history of rheumatic diseases were noted. Complete blood count (CBC) and biochemical profile, complete urinalysis, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), autoantibodies including rheumatoid factor (RF): RF (determined by nephelometric assay, samples with results ≥14 IU/mL were defined as positive), anti-cyclic citrullinated peptide (CCP): Anti-CCP (determined by enzyme-linked immunosorbent assay: ELISA, samples with results ≥20 U/mL were defined as positive), and anti-nuclear antibody (ANA): ANA (determined by ELISA), HLA-B27, serologic tests for hepatitis B virus, hepatitis C virus and brucellosis (which is endemic in the study area) were performed from blood samples. Radiography of the hands, feet, sacroiliac joints, chest, and affected joints were obtained.

The disease activity was assessed by a visual analog scale (VAS: range 0-100 mm), which was rated by evaluating morning stiffness and resting pain; VAS ≤10 mm was defined as remission. Orally (po) low dose methylprednisolone (MP: 4 mg/day), single-dose intra-articular steroid (IAS: triamcinolone hexacetonide), sulphasalazine (SSZ: 1.5 or 2 g/day), methotrexate (MTX: 15 mg/week), leflunomide (LEF: 20 mg/day) were used as treatment options. If arthritis was resistant to conventional synthetic disease-modifying anti-rheumatic drug (csDMARD) monotherapy

(after three months), combined two DMARDs were used. If arthritis was resistant to adequate dose and duration of combined csDMARDs, infliximab (INF: same posology as RA: 3 mg/kg given as an intravenous induction regimen at 0, 2, and 6 weeks, followed by a maintenance regimen of 3 mg/kg at every 8 weeks) was administered as a biological therapy option. VAS and laboratory assessments (including hematologic and biochemical profile, ESR, and CRP) were routinely performed during the follow-up period.

Statistical Analysis

Quantitative variables are expressed as median and ranges (minimum-maximum). Qualitative variables are expressed as proportions. Patient groups with erosion versus no erosion were compared for means using Mann-Whitney U test. For comparisons between proportions, chi-square tests were used. Statistical analysis was performed using SPSS 22.0 version (IBM SPSS, Chicago, IL). A p-value of ≤0.05 was considered statistically significant.

Results

Patients Characteristics

Totally 60 patients enrolled, 77% of the cohort were female and the mean age was 49.7 years. The female-to-male ratio was 3.3/1, the mean disease duration time was 78 months, and the mean follow-up time was 12 months at the end of the study. Thirteen patients (22%) had a family history of rheumatic disease in first or second-degree relatives; there were seven pUA, four peripheral SpA (pSpA), one AS, and one patient with RA. In the first-degree relatives; there were three pUA, two pSpA, and one patient with RA. There wasn't psoriasis history in the first or second-degree relatives, and 31% of patients had a smoking history (active or ex-smoker).

On physical examination; vital signs were normal in all patients, patients did not have redness or warmth at affected joints, and joint swelling was detected in 70% of patients. Biochemical profiles, CBC, and urinalysis were within normal ranges. Serologic tests for hepatitis B virus, hepatitis C virus, and brucellosis were resulted as negative. There wasn't any specific finding were on radiographs, and seven of 60 patients (11%) had severe joint space narrowing in affected joints. Two patients had a positive test for RF (titers with 20 and 15 IU/mL), and both of them had erosive arthritis. Three patients had a positive test for anti-CCP (titers with 46, 22, and 21 U/mL), and one of them had erosive arthritis. Both RF and anti-CCP positivity wasn't detected.

In the study population, 80% of patients had monoarthritis and 20% had oligoarthritis. The most common clinical pattern was (chronic) monoarthritis affecting the knee with a rate of 56.6%. In the follow-up, a clinical switch between mono- and oligoforms or polyarticular joint involvement wasn't observed. The maximum affected joint number was two. The knee was the most affected joint and 42 of 60 (70%) patients had knee involvement. A symmetrical pattern was observed in 17% of patients and all of them had knee or ankle arthritis. Demographic, laboratory, and clinical characteristics are given in Table 1.

Treatment Characteristics

All patients were treated with DMARDs. Treatment regimens including intra-articular or orally low-dose steroids (which were given as an adjunctive treatment) were uncommon. Seven of 60 patients were excluded from the evaluation of treatment efficacy because follow-up time was insufficient. Thus 53 patients were assessed for the treatment results. In most patients (n=49), SSZ monotherapy was employed as an initial treatment and 34 of them achieved remission. First-line MTX monotherapy (n=4) was effective in all patients. Combinations of SSZ+MTX, MTX+LEF, and SSZ+LEF were used in cases when SSZ monotherapy was ineffective. Infliximab was used in three patients who resisted against MTX+SSZ combination; these patients went into remission six months after treatment with Infliximab.

At the end of the study we found out 52 of 53 (98%) patients entered remission; 75% of patients were treated with monotherapy and 23% needed csDMARD combination or INF therapy. Only one patient who did not desire biological agents had an active disease under the SSZ+MTX+IAS combination. Three patients went into remission, and all medications ceased; two of them used INF. Treatment characteristics are given in Table 2.

Comparison of the Erosive and Non-erosive Group

Among all variables, only metatarsophalangeal (MTP) joint involvement was significantly higher in the erosive group (p=0.046). Both RF and anti-CCP were negative in patients with MTP involvement. Demographic, laboratory, and clinical characteristics were not statistically different. A comparison of the erosive and non-erosive groups is given in Table 3.

Discussion

The published studies about UA were usually focused on the early phase of UA (eUA)/early arthritis and defined risk factors predisposing to other rheumatologic diseases, mostly RA. Our study included patients with pUA who had little possibility of developing another rheumatologic disease or go into spontaneous remission because of the long-standing

disease course. We found that the knee was the most affected joint, the ankle was second and the unique results of our study showed that one-third of patients had erosive arthritis. Metatarsophalangeal joint involvement was higher in the erosive group than non-erosive group and 75% of patients had remission with csDMARD monotherapy.

Van der Helm-van Mil et al.[11] found that age, female sex, small joint involvement in hands/feet, symmetric localization, both upper and lower extremities involvement, morning stiffness, number of tender/swollen joints >10, CRP level >50 mg/liter and anti-CCP positivity were found to be independent predictive variables for RA development; anti-CCP positivity and morning stiffness >90 on 0-100 mm VAS were found the strongest among independent variables. The study by van Gaalen et al.[12] supported these results, moreover, anti-CCP was the most prominent predictor for RA development. In another study, RF and disease duration time were found to be independent variables, RF was the strongest independent variable of RA development.[13] The predictive value of anti-CCP was also supported by two Chinese studies.[14,15] In our study, the rate of MTP joint involvement was 8%, RF or anti-CCP positivity rate was only 8%, and two patients had a CRP value higher than 50 mg/liter at baseline. Additionally, both upper and lower extremities involvement, hand involvement, and polyarticular pattern were absent. Both RF and anti-CCP positivity, which were absent in our cases, have high specificity and positive predictive value for RA development in early arthritis.[16]

Fletcher and Scott[17] performed a study that included 151 patients with chronic monoarthritis; they found that the knee was the most affected joint (74.1%), the ankle was second (8%), and nearly all the patients had improvement or complete remission at the end of 129-week follow-up. In a retrospective study of 46 patients with chronic monoarticular arthritis who have 29.5 months mean disease duration time; only one patient-developed pUA at the end of a six-year follow-up, the knee was the most frequently affected

Table 1. Demographic, laboratory, and clinical characteristics

Age, mean (range), years	49.7 (19-74)
Female sex, n (%)	46 (76.7)
Male sex, n (%)	14 (23.3)
Age at onset, mean (range), years	44.3 (18-67)
Disease duration time, mean (range), months	78 (12-192)
Follow-up time, mean, months	12
Family history of rheumatic diseases, n (%)	13 (21.6)
Smoking history, n (%)	19 (31.6)
RF positivity, n (%)	2 (3.3)
Anti-CCP positivity, n (%)	3 (5)
Baseline ESR (mm/h), mean (range)	30 (1-84)
Baseline CRP (mg/L), mean (range)	13.5 (0-216)
Monoarthritis, n (%)	48 (80)
Oligoarthritis, n (%)	12 (20)
Erosive arthritis, n (%)	21 (35)
Joint effusion in physical examination, n (%)	42 (70)
Mean number of active joints, n	1.2
Number of total affected joints, n	72
-Knee, n (%)	49 (68)
-Ankle, n (%)	16 (22)
-Tarsometatarsal joints (TMT), n (%)	2 (3)
-Metatarsophalangeal joints (MTP), n (%)	5 (7)
Clinical presentation	
-Knee monoarthritis, n (%)	34 (56.6)
-Ankle monoarthritis, n (%)	8 (13.3)
-Bilateral knee arthritis, n (%)	7 (11.6)
-MTP monoarthritis, n (%)	4 (6.6)
-Bilateral ankle arthritis, n (%)	3 (5)
-TMT monoarthritis, n (%)	2 (3.3)
-Asymmetrical oligoarthritis (knee+ankle and ankle+MTP joint), n (%)	2 (3.3)

anti-CCP: Anti-cyclic citrullinated peptide, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, MTP: Metatarsophalangeal, RF: Rheumatoid factor, TMT: Tarsometatarsal

joint, the wrist was second, and the SpA was significantly higher in HLA-B27-positive patients. However, the wrist was not an affected joint in our cohort, which could be a target joint in patients with a specific diagnosis.[18] In the report by Blocka and Sibley,[19] two years follow-up of 38 chronic monoarticular UA patients with 20.5 months mean duration of symptoms before referral; 66% of patients remained UA, 10 had spontaneous remission and 16 had pUA (rate of pUA was 42%). The most affected joint was the knee (61%) and the HLA-B27 positivity of the study population was higher than that of the healthy population. The highest rate of pUA (90%) was found in a study from Finland, which consisted of 32 patients with chronic monoarticular UA having 3-9-years follow-up time; HLA-B27 positivity was higher than the healthy population, the knee was the most affected joint (63%), ankle and metacarpophalangeal joint were secondary.[20]

Table 2. Treatment characteristics

Intra-articular steroids (IAS), n (%)	6 (11.3)
Methylprednisolone (MP), n (%)	3 (5.6)
Sulphasalazine (SSZ), n (%)	49 (92.4)
Methotrexate (MTX), n (%)	18 (34)
Leflunomide (LEF), n (%)	2 (3.7)
Infliximab (INF), n (%)	3 (5.6)
Initially DMARD regimen (First-line)	
-SSZ monotherapy, n (%)	49 (92.4)
-MTX monotherapy, n (%)	4 (7.6)
Finally DMARD regimens	
-SSZ monotherapy, n (%)	34 (64.1)
-MTX monotherapy, n (%)	6 (11.3)
-INF, n (%)	3 (5.7)
-SSZ+MTX, n (%)	8 (15.1)
-MTX+LEF, n (%)	1 (1.9)
-SSZ+LEF, n (%)	1 (1.9)

DMARD: Disease-modifying anti-rheumatic drugs

Table 3. Comparison of the erosive and non-erosive group

	Erosive (n=21)	Non-erosive (n=39)	p
Age, median (range), years	51 (35-71)	49 (19-74)	0.299
Sex, n, (%)			
-Male	5/21 (23.8)	9/39 (23)	0.949
-Female	16/21 (71.2)	30/39 (77)	
Arthritis onset age, median (range), years	45 (23-65)	43 (17-67)	0.389
Arthritis duration time, median (range), years	6 (1-16)	4 (1-14)	0.153
Family history of rheumatic disease, n, (%)	5/21 (23.8)	8/39 (20.5)	0.767
Smoking history, n, (%)	7/21 (33.3)	12/39 (30.7)	0.839
Joint effusion in physical examination, n, (%)	17/21 (81)	25/39 (64.1)	0.174
Knee arthritis, n, (%)	15/21 (71.4)	27/39 (69.2)	0.859
Ankle arthritis, n, (%)	4/21 (19)	9/39 (23)	0.718
MTP arthritis, n, (%)	4/21 (19)	1/39 (2.5)	0.046
TMT arthritis, n, (%)	0/21 (0)	2/39 (5.1)	n/a
Joint count, n, (%)			
-Monoarticular	16/21 (71.2)	32/39 (82)	0.588
-Oligoarticular	5/21 (23.8)	7/39 (18)	
ESR (mm/h), median (range)	26 (1-84)	33 (4-70)	0.285
CRP (mg/L), median (range)	6 (0-54)	5 (0-216)	0.773
RF positivity, n, (%)	2/21 (9.5)	0/39 (0)	n/a
Anti-CCP positivity, n (%)	1/21 (4.7)	2/39 (5.1)	0.950

CCP: Cyclic citrullinated peptid, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, MTP: Metatarsophalangeal, RF: Rheumatoid factor, TMT: Tarsometatarsal

Previous studies reported that the knee was the most common target joint in patients with chronic monoarticular UA and our study supported these results, but other affected joints varied; for example, wrist or hip joint involvement was absent in our cases. Joint fluid cytology and synovial histopathology did not have any diagnostic or prognostic value in patients with chronic monoarticular UA. Study design or follow-up time may be a reason for different rates for pUA;[17-20] the mean follow-up time of our study was one year, and the mean disease duration time before referral was 5.5 years. Metatarsophalangeal joint involvement may be confused with gout, but lack of an acute red/warmth articular inflammatory attack history, normal levels of serum uric acid, absence of tophi, and absence of radiographic features for chronic gout arthritis (absence of erosions with overhanging edges and relative preservation of the joint space) were the major clues excluding gout.

The most common diagnosis of patients with oligoarthritis is transient/persistent UA; 40% of them have ankle involvement and the prognosis is generally benign.[21] In our study, the knee and ankle were the two most commonly affected joints as HLA-B27 positive oligoarthritis.[22] Hulsemann and Zeidler[23] reported that the rate of oligoarticular joint involvement in patients with UA was 68% but we found 20%; discordance is probably the result of higher RF and HLA-B27 positivity rates than our study population. In an early arthritis study with 524 patients who had two-year follow-up time; the rate of pUA was 6%, and the frequency of erosive arthritis of patients with pUA was 25% that was lower than our study.[24]

MRI is more sensitive than clinical examination and radiography detecting synovitis, tenosynovitis, enthesitis, and bone erosions for inflammatory joint diseases so MRI detects more bone erosions than radiographs but sometimes small bone erosions may be found in the metacarpophalangeal and wrist joints of healthy controls.[25,26] In a study assessing knee by MRI, patients with RA showed more destructive changes (e.g. synovial thickening, bone marrow edema, cartilaginous and bone erosions) than patients with UA and SpA; bone erosion was present in 16% and enthesitis 12% in patients with UA, additionally, there was no correlation between disease duration and MRI findings.[27] In knee MRI images, we didn't find enthesitis and we found a frequency of erosive arthritis of 36%. We didn't detect any erosion on hands/feet or affected joint radiographs, moreover baseline hand/feet erosions on radiography are not predictive for poor prognosis at all time.[28]

The treatment of pUA is still unknown. In a double-blind, randomized, placebo-controlled study (PROMPT study) including patients with UA; methotrexate showed beneficial effects on radiological progression but disease duration time was shorter than one year, RF and anti-CCP positivity rates were 36% and 22% respectively.[29] We generally preferred to use SSZ as a first-line csDMARD, which is a well-known anti-rheumatic drug in daily practice and effective for treating RA and SpA;[30] at the end of our study, 34 of 53 patients had remission with SSZ monotherapy. Saleem et al.[31] reported that INF had positive effects on CRP and health assessment questionnaires but was not effective in preventing the development of RA in patients with RA. INF was the single biologic agent which was chosen because of its implementation at the hospital so we managed full harmony in therapy and all of INF administered patients had remission. Abatacept showed beneficial effects on radiological progression and reduced anti-CCP levels in some patients with UA/very early RA whom RF and anti-CCP positivity rates were 90.9% and 85.7% respectively.[32]

There are different results in different studies for patients with UA because the study design, follow-up time, and disease duration time are variable. RA incidence increases and UA incidence decreases with increasing disease duration time.[33] Patients with pUA have lower ESR levels, and less active and eroded joint count; social and functional prognosis is better than patients with RA.[34] Smoking is associated with poor outcomes in patients with RA and SpA;[9] the smoking history of our patients was similar between the erosive and non-erosive groups (p=0.83).

Study Limitations

The absence of HLA-B27 in 20 of 60 patients (because of technical incompetence), the short follow-up period despite the long disease duration time, and the small sample size were the limitations of our study. The lack of synovial biopsy may be another limitation, but 98% of patients had remission with DMARD treatment, so we didn't consider any non-rheumatic condition in the differential diagnosis. Additionally, synovial biopsy has little diagnostic and prognostic value in undifferentiated peripheral inflammatory arthritis.[35]

Conclusion

Consequently, our patients with pUA showed some unique characteristics such as female sex predominance and (sometimes) erosive arthritis like RA, mono/oligoarticular involvement-like SpA, low positivity rates for RF of anti-CCP, and absence of clinical switch. Family history of rheumatologic disease, chronic disease course, and good response to DMARDs were similar features to other articular rheumatologic diseases. Most of the patients had a good response to csDMARD monotherapy, but erosive disease

course and long lag time until diagnosis was the real problem. Absence of extra-articular manifestations (such as psoriasis, subcutaneous nodules, or interstitial lung disease), low positivity rates of auto-antibodies, mildly elevated ESR and CRP, symptoms falsely considered as gonarthrosis by other physicians before exact diagnosis, and lack of knowledge about pUA could be the reasons for late diagnosis. There are limited data for patients with pUA in the literature so we believe that the results of our study can bring benefits in daily rheumatology practice. A new rheumatological disease will be defined in the future by increasing knowledge about pUA.

Ethics

Ethics Committee Approval: The study was approved by the ethics committee of the University where the study was conducted (Mus Alparslan University Ethics Committee - approval number: 7351; date: 07.04.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: No conflict of interest was declared by the author.

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