



The frequency and associated factors of erosive osteoarthritis in patients with rheumatoid arthritis

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Abstract

Erosive osteoarthritis (EOA) is a deformative joint disease affecting small joints of hands that causes pain and disability, as does rheumatoid arthritis (RA). So, EOA may interfere with the assessment of RA disease activity. In this study, we aimed to determine the frequency and associated factors of EOA in patients with RA and pay attention to the overlap syndrome between RA and EOA. The electronic medical files of adult RA patients were reviewed retrospectively. Patients with another rheumatic diseases were excluded. Hand X-rays were read by two rheumatologists and one radiologist. Patients with RA were divided into two groups according to the presence of EOA. We totally analyzed 619 patients with a mean age of 54.2 years, and 82.8% of them were female. The 95.4% of patients had RA-type erosive changes according to the Modified Sharp Score. We found the frequency of EOA to be 6.3% in patients with RA. Erosive osteoarthritis was significantly higher in patients who had >50 years of age ($p=0.006$), disease duration >10 years ($p=0.003$), and anti-CCP negativity ($p=0.02$) than in those without. In multivariable regression analysis, only age was the independent predictive factor for EOA ($p<0.001$) in RA patients. We published the frequency and associated risk factors of EOA in RA for the first time in literature. Rheumatologists should take EOA into account when making treatment decisions in middle aged/elderly RA population. Further prospective studies are needed to explain the linkage between RA and EOA.

Keywords: erosive osteoarthritis, rheumatoid arthritis, risk factor, overlap syndrome

1. Introduction

Erosive osteoarthritis (EOA) is a subtype of hand osteoarthritis (HOA) and has different radiological and clinical features from other forms of HOA (1). The frequency and localization of joint involvement are similar between EOA and non-erosive HOA, but EOA has worse radiological outcomes (2). In 1961, Crain DC described 23 middle-aged women with 'interphalangeal osteoarthritis' who had acute inflammatory arthritis attacks and hand deformities in interphalangeal (IP) joints (3). The term of EOA was first described by Peter JB et al. in 1966 (4). Clinical features of EOA are characterized by acute inflammatory polyarticular attacks in IP joints; pain, joint effusion, warmth, and erythema generally occur; nevertheless, morning stiffness is shorter than 30 minutes. Patients with EOA have a mean age of nearly 50 years at the disease onset, and the female-to-male ratio is 7/1 (5). The distal interphalangeal joint (DIP) is the most frequently affected joint, followed by the proximal interphalangeal joints (PIP); the most commonly involved fingers are the second and third in a symmetric pattern (6). The European League Against Rheumatism (EULAR) Task Force identifies the first IP joints and the first carpometacarpal (CMC) joints as the primary target joints for EOA (1). Erosive osteoarthritis is characterized by central subchondral erosion and marginal osteoproliferation

in hand X-ray (7). The central erosions can lead to 'gull-wing' or 'saw-tooth' signs, especially in DIP or PIP joints, and joint ankylosis occurs in 15% of patients with EOA (8). Blood tests are not required; posteroanterior hand X-rays are adequate for diagnosing EOA (1).

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune, and inflammatory joint disease with a prevalence of 0.5–1%. Polyarticular, symmetrical, and erosive joint involvement are the typical features of RA (9). Rheumatoid arthritis primarily affects the peripheral small joints, with hand involvement occurring in 90% of patients, whereas DIP involvement is uncommon (10). Radiologically, these two diseases are very different. Rheumatoid arthritis is characterized by marginal erosion and the absence of osteoproliferation. However, joint subluxation and ankylosis are the most prevalent features in RA (5). Small joint arthritis of the hand (especially in PIP joints), symmetrical pattern, and erosive/deformative course are the common features of EOA and RA.

The 2010 American College of Rheumatology (ACR)/EULAR RA classification criteria include metacarpophalangeal (MCP) joints, PIP joints, and wrists,

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excluding DIP and first CMC joints due to their overlap with osteoarthritis. Furthermore, a great number of peripheral arthritic joints are associated with classifying patients as having RA (11). The disease activity-28 scoring system (DAS-28), the most common method for assessing the disease activity in RA, evaluates the first IP and PIP joints, which are commonly affected in both RA and EOA (12). A miscalculated DAS-28 score is a possible scenario in patients with RA accompanying EOA.

Rheumatologists need to be aware of the EOA in patients diagnosed with RA. It is crucial for clinical practice and disease management to identify the frequency of EOA, and risk factors in RA patients. These issues are currently unknown and await exploration. Previous studies have focused on non-erosive forms of OA in RA (13, 14). No information regarding the overlap syndrome between RA and EOA has been identified in the medical literature. This study aims to investigate these issues, with the expectation that our findings will improve the accuracy of RA disease management.

2. Material and Methods

2.1. Data collection and patients' selection

We consecutively analyzed the patients with RA who were regularly following up in our tertiary outpatient rheumatology clinic. Electronic medical records were reviewed retrospectively; demographic, clinical, laboratory, and treatment data were noted between July 2021 and December 2021. All patients fulfilled the 2010 ACR/EULAR RA classification criteria (11), and were aged 18 years or older. Exclusion criteria were absence of a hand X-ray within the last year, having lost a large portion of the finger, and overlapping with another rheumatologic disease that can cause erosions/deformities in DIP or PIP joints, such as systemic sclerosis (12), psoriatic arthritis (13), anti-Jo1 syndrome (14), gout (15) and calcium pyrophosphate deposition disease (16). The diagnosis of EOA was based on EULAR evidence-based recommendations for the diagnosis of HOA [1].

2.2. Assessments

Radiological findings were evaluated according to the Modified Sharp Score (MSS) on patients' hand X-rays within the last year. Rheumatoid arthritis type joint involvement (RJI) was defined by the presence of erosion or joint space narrowing (JSN). 'Severe joint involvement (SJI)' was defined by the presence of erosion with a score of ≥ 3 points or JSN with a score of ≥ 4 points as per the MSS (17). Radiological erosion of hand osteoarthritis was defined by the presence of an eroded (E) or remodeled (R) phase of the Verbruggen-Veys anatomical progression score in IP joints (18). Each x-ray was read by two rheumatologists (MP, SK) and one radiologist (IK), separately. All readers were blinded to the patients. If there was no agreement between readers, X-rays were re-assessed, and then a final common decision was made with full agreement.

Rheumatoid factor (RF) was measured by nephelometric assay, and serum samples with results ≥ 14 IU/ml were defined as positive. Anti-cyclic citrullinated peptide antibody2-IgG (anti-CCP) was measured by enzyme-linked immunosorbent assay (ELISA), and serum samples with results ≥ 5 U/ml were defined as positive. Smoking history (active or ex), and biologic or target synthetic disease modifying antirheumatic drug (b/tsDMARD) use (active or ex) were also noted.

2.3. Statistical analysis and ethical standards

The chi-squared and Fisher's exact test were used to analyze categorical data and independence between variables. Binary logistic regression was utilized to predict EOA using age, gender, disease duration (>5 years, >10 years), RF positivity, and anti-CCP positivity as predictors.

3. Results

A total of 635 patients were reviewed; 12 patients were excluded due to the absence of a hand X-ray, three were excluded due to overlapping with another rheumatic diseases, and one was excluded because of losing a large portion of a finger. No patient had a family history for psoriasis. We analyzed a total of 619 patients; 83.3% of them were female, the mean age was 54.2 ± 12.6 years, and the mean disease duration time was 8.3 ± 7.7 years. Rheumatoid factor and anti-CCP positivity were 58.4% and 56.7%, respectively. The 66.5% of patients were seropositive (RF alone, anti-CCP alone, or both RF and anti-CCP positive). The authors re-reviewed 116 of 619 hand X-rays, and made the final decision; 94.3% of patients had RJI, 23.2% had SJI, and 6.3% had EOA (Fig. 1 shows an example of overlap syndrome between RA and EOA). Table 1 shows the demographic, laboratory, and treatment characteristics of the study group.

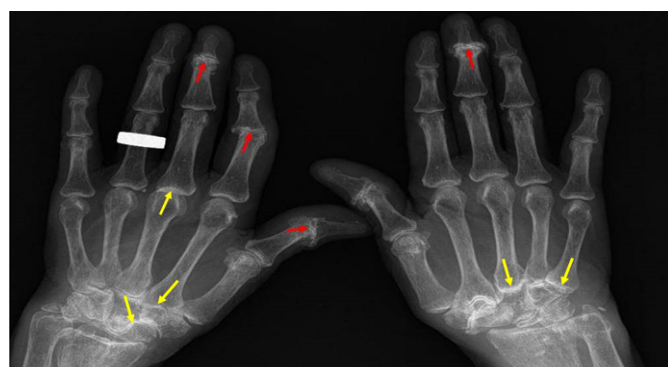


Fig. 1. Changes due to EOA (red arrow) is observed in the third distal interphalangeal joints, first finger interphalangeal joint, and in second proximal interphalangeal joint. The RA-type narrowing (yellow arrow) is present at the third metacarpophalangeal joint and multiple carpo-metacarpal levels

The localization areas of EOA in DIP, PIP, and IP joints were 55.1% ($n= 86$), 27.6% ($n= 43$), and 17.3% ($n= 27$), respectively. The 1st IP and 3rd DIP joints were the most commonly affected joints by EOA; the 4th PIP joints were the least. Table 2 shows the radiological features of EOA.

Table 1: Demographic, laboratory, and treatment characteristics of patients

Variable	Total patients (n= 619)
Age, mean ±SD, years	54.2 ±12.6
Female sex, % (n)	83.3 (516)
Male sex, % (n)	16.7 (103)
Disease duration, mean ±SD, years	8.3 ±7.7
Smoking history, %, (n)	31.5 (195)
RF positivity, %, (n)	58.3 (361)
Anti-CCP positivity, %, (n)	56.7 (351)
RJI, %, (n)	94.3 (584)
SJI, %, (n)	23.2 (144)
b/tsDMARD use, %, (n)	35.2 (218)

SD, standard deviation; RF, rheumatoid factor; anti-CCP, anti-cyclic citrullinated peptide antibody; RJI, Rheumatoid arthritis type joint involvement; SJI, serious joint involvement; b/tsDMARD, biologic or target synthetic disease modifying antirheumatic drug

Table 2: Radiological analysis of EOA findings

Patients with EOA, n (%)	39 (25)
Total affected joint count, n	156
Mean affected joint, n (min-max)	4 (1-17)
Localization of EOA	
-1st IP joint, n	27
-2nd DIP joint, n	26

Table 3. Comparison of patients with and without erosive osteoarthritis

Variable	EOA- group (n= 580)	EOA+ group (n= 39)	P value
Female sex, %, (n)	84 (485)	80 (31)	0.506
Age >50 years old, %, (n)	63 (366)	85 (33)	0.006
Disease duration > 5 years, %, (n)	56 (327)	69 (27)	0.134
Disease duration > 10 years, %, (n)	28 (163)	51 (20)	0.003
Smoking, %, (n)	32 (186)	9 (23)	0.287
RF positivity, % (n)	59.5 (345)	41 (16)	0.06
Anti-CCP positivity, %, (n)	57.9 (336)	38.5 (15)	0.02
Serious joint involvement, % (n)	24 (139)	12.8 (5)	0.557
Biologic agent use, %, (n)	34.8 (202)	41 (16)	0.487

EOA, erosive osteoarthritis; RF, rheumatoid factor; anti-CCP, anti-cyclic citrullinated peptide antibody

4. Discussion

Our research is the first study conducted so far investigating EOA in patients with RA. We found the frequency of EOA to be 6.3%, and age was an independent predictive factor for developing EOA in patients with RA. Moreover, RA patients with an age >50 years, disease duration >10 years, and anti-CCP negativity tended to have EOA. The prevalence of EOA is 2.8% in the general middle-aged population so our results suggest that patients with RA may be more susceptible to developing EOA (19).

Rheumatoid arthritis, and EOA have some common risk factors, such as female sex, obesity, and the IL-1β-associated genes, which may lead to an enhanced frequency of EOA in RA (20-24). Inflammation, and cartilage damage play a role in the pathogenesis of EOA, affecting the synovium, bone, and cartilage, which are all interrelated tissues in both RA and OA (7, 25, 26). Common histopathological findings on synovial biopsies include synovial cell hyperplasia, round cell infiltration, and pannus; however there are distinct synovial histological differences between EOA and RA (27, 28). Rheumatoid arthritis has a chronic and progressive course which may explain the relationship between the disease duration of RA and EOA. The 2010 ACR/EULAR RA classification criteria includes anti-CCP antibody positivity

-3rd DIP joint, n	27
-4th DIP joint, n	13
-5th DIP joint, n	20
-2nd PIP joint, n	13
-3rd PIP joint, n	11
-4th PIP joint, n	7
-5th PIP joint, n	12

EOA, erosive osteoarthritis; IP, interphalangeal; DIP, distal interphalangeal; PIP, proximal interphalangeal

Erosive osteoarthritis was significantly higher in patients who were >50 years old (p= 0.006), had a disease duration time of RA >10 years (p= 0.003), had anti-CCP negativity (p= 0.02) (Table 3). The mean age was significantly higher in patients with EOA (62.9 vs. 53.6; p<0.001), and the mean disease duration time of RA was significantly higher in patients with EOA (12.5 vs. 8 years, respectively; p<0.001) than in patients without EOA. In the multivariate regression analysis model (including sex, age, disease duration time >5 years, disease duration time >10 years, RF, and anti-CCP), only age was the independent predictive factor for EOA (p<0.001, odds ratio= 0.938 [0.910–0.967], 95% CI).

(11). Also, anti-CCP positivity rate is 2.1% in non-rheumatic conditions, and can be detected in other autoimmune rheumatic diseases (29). Additionally, both anti-CCP, and RF is not associated with erosive disease, structural damage, or inflammation in patients with HOA (30). Our results supported the previous study.

Serum C-reactive protein (CRP) levels are higher in EOA patients than in non-erosive HOA patients, which correlates with active joint counts and presumably reflects the disease activity of EOA (31). Morning stiffness of <30 minutes is frequent in EOA, which may affect the patient's global health score (3). As a result, EOA can affect both laboratory and clinical parameters of the DAS-28 scoring system in patients with RA. Miscalculated DAS-28 scores may lead to unnecessarily increased biological agent use in patients with RA, but biological agent use was not statistically different between the EOA (+) and (-) groups (34.8% vs. 41%, respectively) in our study population. Many synthetic, biological, and target synthetic DMARDs are effective in the treatment of RA (32), but there is no indicated DMARD for the treatment of EOA (1).

Currently, published studies focused on EOA and inflammatory rheumatic diseases, except for RA (33-35). Avouac J et al. investigated radiological hand involvement in

patients with SSc (n= 120), and found the frequency of EOA as 15% (33). Baron M et al. investigated articular manifestations of progressive SSc (n= 38) and found the frequency of EOA as 18% (34) but both of two study's population were generally post-menopausal women who tend to develop EOA (28, 29). In a study from Turkey (n= 114, with a mean age of 51 years old, and 96.4% of them were female), Aksoy et al. found the frequency of EOA as 16% and 0% in patients with Primary Sjogren Syndrome and systemic lupus erythematosus respectively but the healthy control group was absent (35). A nationwide population-based cohort study from Taiwan found an increased risk of osteoarthritis in patients with RA. However, this study did not provide data on EOA or other subtypes of hand OA (10). In a prospective study, Erlich GE reported that 15% of patients with inflammatory osteoarthritis developed RA during follow-up, especially within five years of onset (4).

Despite remarkable results, our study had some limitations, such as a retrospective design, the absence of a healthy control group, and a lack of body mass indexes. Inter- and intra-observational agreement is another important limitation. In some cases with established RA, ankylosed joints couldn't be evaluated for EOA because the normal joint structure was totally damaged or joint ankylosis due to EOA may have assessed as SJI.

In conclusion, we found the frequency of EOA in patients with RA to be 6.3%, and only age is an independent risk factor for EOA. The mean age, and disease duration were significantly higher in patients with EOA than those without EOA. As a matter of fact, rheumatologists should be aware of the EOA in patients with RA. We first reported the results on this topic in the medical literature. We hope that our results could draw attention to EOA in patients with RA, especially in the middle-aged and elderly population, and could prevent the unnecessarily enhanced DMARD therapy, which is associated with increased treatment complications, toxicity, and cost. Further and prospective studies are needed to demonstrate the linkage between RA and EOA.

Conflict of interest

The authors declared no conflict of interest.

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None to declare.

Authors' contributions

Concept: M.P., Design: M.P., S.K., Data Collection or Processing: M.P., S.K., I.K., Analysis or Interpretation: M.P., S.K., I.K., Literature Search: M.P., I.K., Writing: M.P., S.K.

Ethical Statement

Approval was obtained from Hatay Mustafa Kemal University Tayfur Ata Sökmen Faculty of Medicine Clinical Research Ethics Committee, the study started. The ethics committee

decision date is 14/02/2022 and the number of ethical committee decisions is 2022/21.

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