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An autumn tale: geriatric rheumatoid arthritis

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Abstract: Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by erosive arthritis and systemic organ involvement. The disease may affect all ages and both sexes; usually it is seen in young women aged 25–45. Recent studies have shown that RA is among the most common inflammatory disease in older age groups. While elderly-onset rheumatoid arthritis (EORA) is still discussed in the literature, it is generally accepted as a disease beginning after 65 years of age. Compared with young-onset rheumatoid arthritis (YORA), it was found that EORA had different characteristics. EORA is characterized by more equal gender distribution, higher frequency of acute onset with constitutional symptoms, more frequent involvement of large joints, and lower frequency of rheumatoid factor (RF) positivity. Earlier diagnosis, less erosive disease and less disease-modifying antirheumatic drug usage were reported as distinguishing EORA from YORA patients. These various clinical presentations may cause difficulties in diagnosis and differential diagnosis of EORA. However, different clinical and treatment approaches may be needed in these patients. In this article, the clinical and laboratory characteristics, prognosis and treatment principles of EORA will be discussed in light of recent literature data.

Keywords: characteristics, elderly onset, rheumatoid arthritis

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Introduction

Geriatric rheumatology is a field of science examining the rheumatic diseases affecting older age groups. Physiological and immune system changes seen in the geriatric population may be the reasons for frequent and different presentations of inflammatory rheumatologic diseases in this age group. In recent years, we have understood that rheumatologic diseases show some differences in different age group populations. We noticed that these diseases, which mostly affect the young population, may be seen in a large proportion of older age groups. Rheumatoid arthritis (RA) is a multisystemic, chronic inflammatory disease characterized by destructive synovitis. It can affect all joints, but mainly involves the small joints of the hand and foot with erosive changes. RA is a progressive chronic disease resulting in decreased functional capacity and quality of life, increased morbidity and mortality.[1] It can be seen in all ages and in different ethnic populations, but the prevalence of the disease increases with age and is seen in 2% of the geriatric population.[2] Although the terminology in the literature is not clear, generally disease that starts after 65 years of age is known as elderly-onset RA (EORA). There are different population-based studies of EORA incidence and prevalence. The annual incidence rate of EORA in the world may vary widely, depending on sex and ethnicity.[3] According to a study in Spain, the incidence rate of RA per 100,000 population over the age of 60 was found to be 9.1 in men and 14.5 in women.[4] Again, in a study conducted in the USA, the prevalence of RA was 0.5–1%, while it was found to be 2% in the population over 60 years.[5] According to the Norwalk Arthritis Research (NOAR) database in the UK, as age increases, the incidence of RA also increases.[6] Compared with young-onset RA (YORA), the ratio of women/men in EORA is also reduced (4/1 *versus* 2/1). As the expectation

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of life in developed countries increases, the number of people over 65 years in the general population is rapidly increasing. This fact will likely increase the number of patients with EORA in the coming years.

In this review, the clinical characteristics, prognosis and treatment principles of EORA will be discussed in light of recent literature data.

Genetics

RA develops in individuals with a genetic predisposition. The best known genetic association in RA is the DRB1 locus in the HLA class 2 gene. The RA-associated DRB1 alleles share a linear sequence of amino acids between positions 70 and 74 in the HLA-DRB1 chain of the HLA-DRa/b heterodimer, which has led to the 'shared epitope' (SE) hypothesis.[7] Having a SE is a risk factor for RA development. Jnhi DRB1 allele was associated with early onset of disease, radiological erosion and extra-articular findings.[8] The results of studies investigating genetic predisposition in EORA are inadequate and contradictory.[9] RA-associated DRB1 alleles show differences in early and late onset RA as well as ethnic variants. In a study conducted in Spain, it was found that YORA was related to DRB1/04, while EORA was associated with DRB1/01.[10] In addition, increased DRB1-13/14 frequency was detected in patients with seronegative EORA and polimyalgia rheumatica (PMR). In another prospective study, a relationship was found between PMR and DRB1 * 0101/0102/0401 while seronegative EORA was associated with DRB1-0401. Kim and colleagues investigated the impact of HLA-DRB1 and HLA-DQB1 genes on susceptibility to disease and disease severity in EORA and YORA patients.[11] Alleles encoding the common epitope were detected less frequently in EORA compared with YORA (49.2% *versus* 66.1% respectively). In EORA susceptibility, the effect of the common epitope and HLA-DQ * 04 alleles was shown to be less significant. Compared with YORA, EORA has also been found to have less common epitope presence and less radiological progression. Hellier and colleagues investigated the effect of the HLA-DRB1 gene on disease susceptibility and disease severity in EORA and YORA.[12] Compared with YORA, HLA-DRB1/04-related alleles were not closely associated in EORA. The impact of these genes on the susceptibility to disease in EORA suggests that it is not very important. Wu and colleagues showed that the DRB1/04 allele was detected in half of the EORA population while the DRB1/04 frequency was 92% in patients with RA starting before 30 years of age.[13]

Pathogenesis

The clinical, genetic and laboratory differences between EORA and YORA are not understood yet but the immunological and hormonal changes in the geriatric population may be speculated. Senility is a physiological process characterized by reduced T-cell proliferation, reduced antibody synthesis to vaccination, and elevated proinflammatory cytokine levels.[14] Immune system changes include T-cell phenotype alteration, reduction in specific immune response, apoptosis defects, cytokine imbalance, and inadequate antigen presentation. With increasing age, there is a decrease in the protective immunological response, while the reaction to autoantigens is increasing.[15] In addition, self-tolerance mechanism disorders occur. As a result of thymus involution in senescence, changes in T-cell composition, decrease in T-cell proliferation and cytokine synthesis, as well as decreased antibody synthesis after vaccination were seen. In one study, elevated interleukin (IL)-6 secretion was associated with dehydroepiandrosterone and androstenedione synthesis in patients with EORA.[16] The acute onset and increased acute phase response seen in EORA may be explained by increased IL-6 levels. Punzi and colleagues showed elevated IL-6 in the EORA synovial fluid compared with YORA, while no differences were detected in IL-1 and IL-8 levels.[17] Different immunoregulatory mechanisms may be at work in the pathogenesis of RA seen in different age groups. Gamerith and colleagues showed a significantly increased anti-IgG-Fab/free aFab ratio in patients with YORA, compared with EORA, leading to increased rheumatoid factor (RF) presence.[18]

Clinical features

EORA is a heterogeneous disease characterized by three distinct clinical patterns.[19,20] The most common clinical form (70%) is similar to classical RA, with RF positivity, joint erosions and worse prognosis than YORA. The second form (25%) is a PMR-like form, with proximal limb joint involvement. It is usually RF negative, has acute onset, does not make joint erosions and has good prognosis. Asymmetric nonerosive polyarthritis may occur in 25% of patients with PMR, so differential diagnosis should be performed well.[21] Anti-cyclic citrulinated peptide (Anti-CCP) antibody positivity in

EORA and bilateral subacromial bursitis in PMR are helpful in this respect. However, the presence of metacarpophalangeal (MCP)/proximal interphalangeal (PIP) joint arthritis with proximal limb joint involvement is considered a predictive factor for seronegative EORA. The third EORA pattern is characterized by clinical and prognostic similarity to RS3PE syndrome.[22] The RS3PE-like form is characterized by sudden onset, wrist tenosynovitis, common pitting edema in the hands, and spontaneous remission within 3–18 months. Interestingly, in these subgroup cases, high HLA-B27 positivity was also reported. The differential diagnosis of EORA is not limited to PMR; other diseases such as crystal arthritis, septic arthritis, sarcoidosis and hepatitis C should also be excluded.[23] In many studies, clinical, laboratory and radiological features of EORA and YORA were compared.[24,25] In EORA, simultaneous small and large joint involvement is frequently seen at the onset of the disease. RF and anti-CCP positivity are seen at similar and/or slightly lower rates compared with YORA. In some studies, higher disease activity scores, serum erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels were reported in EORA. EORA has been shown to be a different clinical entity, characterized by large joint involvement, acute onset pattern, marked constitutional symptoms and spontaneous remission, usually within 18 months. Deal and colleagues compared the characteristics of patients with 78EORA and 134YORA.[26] Acute onset, PMR-like symptoms, less rheumatoid nodule and RF positivity were detected in EORA compared with YORA. Patients with EORA had a lower joint score and a higher Health Assessment Questionnaire (HAQ) score. Türkçapar and colleagues reported the clinical and demographic characteristics of Turkish patients with EORA.[27] Shoulder joint involvement was more frequent in EORA, while PIP, MCP, elbow and ankle joint involvement were more common in YORA. RA deformities, Sjögren syndrome (SjS) and lung involvement are less common in EORA. However, weight loss, myalgia, lymphadenopathy and PMR-like symptoms were more frequent in EORA. When the antibody profile (RF, ANA, anti-Ro, anti-La) was detected less frequently in EORA, chronic disease anemia, ESR and CRP elevation were more common. Similar findings have also been reported by van der Heijde and colleagues.[28] Patients with EORA had more frequent acute onset, initially small and large joint involvement, PMR-like patterns and radiological narrowing of the joint space. Lance and colleagues reported an aggressive, destructive EORA form that makes radiographic erosive changes.[29] These patients are characterized by polyarticular small joint involvement, rapid progression, hand/wrist erosions and early hand function loss. In addition, 63% of these patients reported secondary SjS compared with 25% in patients with YORA.

Laboratory findings

Different and controversial results have been reported in the literature regarding laboratory findings in patients with EORA. In many studies, lower hemoglobin and higher ESR and CRP were detected in EORA compared with YORA.[30] Again, conflicting information is available regarding RF and anti-CCP antibody positivity. In some studies, RF and anti-CCP antibody positivity were reported less frequently in EORA, while in other studies the frequency of these antibodies was found to be similar in both groups.[15,25,28] The variability of these antibodies may be another reason or may explain the different clinical course and prognosis seen in different age groups. However, antibody positivity may be an important prognostic factor. Chen and colleagues compared the proinflammatory cytokine levels of patients with EORA and YORA.[31] Compared with YORA, higher levels of IL-6 and lower levels of tumor necrosis factor α (TNFα) were detected in EORA. Higher IL-6 levels were detected in patients with EORA and PMR-like symptoms. Multivariate analysis showed that high IL-1 levels were associated with anti-CCP antibodies while high TNFα levels were associated with constitutional symptoms in patients with EORA. Compared with YORA, acute onset, constitutional symptoms and comorbid diseases were more frequent in patients with EORA.

Prognosis

There is not enough information in the literature about the clinical course and prognosis of EORA. Some studies show a better prognosis compared with YORA, while others report that they are similar or worse. The above contradictory results may be due to different disease duration between groups examined; bias in patient selection; and different frequencies of seropositivity between younger and older patients. However, the studies investigating the prognostic factors in EORA are not sufficient. In one study, persistent arthritis was seen in 39% of seropositive patients, while in seronegative patients this rate was only 6%.[32] In another study, more swollen joints, radiological damage

and mortality were reported in seropositive patients compared with seronegative patients.[33] In other words, RF and anti-CCP antibodies are considered poor prognostic markers in patients with EORA. Krams and colleagues compared the characteristics of patients with EORA and YORA in the ESPOIR cohort containing 681 patients with RA.[34] At the end of the first year, the SDAI remission rates were higher in the patients with YORA than those with EORA. At the end of the first year, more erosion and high HAQ scores were observed in patients with EORA. As a result, at the end of the third year, patients with YORA had higher remission rates, less radiographic progression and lower HAQ scores compared with patients with EORA. Soo-Kyung Cho and colleagues evaluated 3169 Korean patients with RA.[35] The 486 patients with RA that started when they were over 60 years old were considered to have EORA and were compared with patients with YORA. Late onset RA has been found to be an independent risk factor for functional disability. There are conflicting data regarding the onset of acute disease and prognosis in EORA. In one study, the presence of acute pitting swelling in the hands at the onset of the disease was shown to be a good prognostic factor.[36] Patients with EORA presenting with pitting edema have fewer erosions developing compared with patients with EORA without pitting edema. The literature data on EORA mortality are limited. In one study, there was a statistically significant increase in mortality rates in patients with seropositive EORA compared with the general population.[30] However, there was no such difference in patients who were seronegative.

Differential diagnosis

The differential diagnosis of EORA should be done thoroughly with inflammatory and noninflammatory rheumatic diseases which are frequently seen in this age group (Table 1). Also paraneoplastic and infectious arthritis should be taken into consideration.[37] A very good anamnesis, physical examination, laboratory and imaging methods should be used. Gout arthritis causes intermittent and self-limiting arthritis. Usually it involves one MTP joint, but sometimes it is presented with polyarticular involvement.[38] Radiologically, periarticular osteopenia, typical of RA, is not an expected finding in gout arthritis. Erosions may occur in both diseases, but marginal erosion is typical in RA, whereas erosions with sclerotic margins remote from the joint are seen in gout arthritis. Calcium pyrophosphate dihydrate crystal disease (CPPD) may be present with RA-like polyarticular involvement.[39] Detection of chondrocalcinosis by radiography or detection of crystals in synovial fluid analysis supports the diagnosis of CPPD. PMR is a painful syndrome affecting the shoulder and hip regions.[40] Asymmetric, nonerosive synovitis can occur in 25% of patients and can be confused with seronegative EORA. Unlike EORA, small joint involvement, rheumatoid nodules and anti-CCP antibodies are not detected. Imaging methods (presence of subacromial bursitis on ultranosonography (USG)/magnetic resonance in PMR and erosive changes in EORA) are also helpful in differential diagnosis.[41] RS3PE syndrome is characterized by seronegative symmetric synovitis and pitting edema in the hands or feet.[42] It generally has a good prognosis and responds well to low doses of corticosteroids (CS). Sometimes it can be accompanied by PMR and EORA and should be considered in the differential diagnosis of these diseases. Generally, RF and anti-CCP are negative and no erosion is seen. Osteoarthritis is a degenerative disease that is the most common disease in elderly patients.[43] It usually involves one carpometacarpal (CMC) joint, distal and proximal interphalangeal and knee joints and may present with pain, morning stiffness and restriction of motion. Radiologically it is characterized by osteophytes, joint narrowing and subchondral sclerosis.

Table 1. Differential diagnosis of elderly-onset rheumatoid arthritis.

Osteoarthritis
Polymyalgia rheumatica
Crystal arthritis (gout, pseudogout or chronic pyrophosphate arthropathy)
Remitting seronegative symmetrical synovitis with pitting oedema (RS3PE syndrome)
Spondyloarthropathy
Connective tissue disease
Systemic vasculitis
Paraneoplastic syndrome
Hypertrophic osteoarthropathy
Sarcoidosis
Infectious arthritis (viral and bacterial infections)

Treatment

In recent years, new treatment modalities have been developed which have revolutionized the treatment of RA. Early diagnosis, early administration of disease-modifying antirheumatic drugs (DMARDs) and targeted strategies have been able to prevent radiological progression, reduce morbidity and mortality, and increase functional capacity.[44] The main goal of RA treatment is to control the disease. Treatment of EORA should not be so different from the treatment of YORA. The goal of treatment should be complete remission or low disease activity based on the principles of treat-to-target strategies. DMARDs used in YORA may also be safely used in the treatment of EORA. However, drug pharmacokinetics and pharmacodynamics in the elderly population are different and the drug side-effect profile should be closely monitored.[45] In addition, the incidence of different comorbid diseases has increased in this age group and due to the high number of medications used, caution must be taken in terms of side-effect profile.[46] The literature data on the use of DMARDs in patients with EORA are limited and contradictory, but according to a general understanding, these patients are receiving less aggressive treatment. Data from patients with EORA in the CORONA database were compared with those of age- and sex-matched patients with YORA.[47] Disease activity and disease severity were similar in both groups. Methotrexate (MTX) use was found to be higher in patients with EORA compared with those with YORA (63.9% *versus* 59.6%), while mean MTX dose was found to be higher in patients with YORA. The number of patients using multiple conventional DMARDs or biological DMARDs was found to be lower in those with EORA compared with YORA. Treatment-related toxicity was similar in both groups, whereas toxicity due to MTX was found to be more frequent in the case of YORA. In conclusion, despite similar disease duration, disease activity, and severity, patients with EORA used combined conventional DMARDs and biological DMARDs less frequently compared with patients with YORA. Age of onset determines the severity of the disease and the choice of treatment.[48] anticyclic citrulinated peptide antibody (ACPA) positivity, erosions, high Larsen scores, disease activity and HAQ scores were found more frequently in patients with YORA compared with those with EORA. Also, patients with YORA started DMARDs earlier, whereas patients with EORA received more CS and fewer DMARDs and biological therapy. As a result, the age of the patient determined the choice of treatment and this may be influential for the development of comorbidities. Elderly patients use MTX at lower doses and as a single agent. In this age group, more CS, fewer DMARDs and less biological use is a striking finding. According to Swiss registries, the use of first-line CS was significantly higher (25.5% *versus* 68%) in patients with EORA compared with those with YORA, while the use of biological drugs during follow up was much lower.[49] Genevay and colleagues evaluated 1571 patients with RA (344 over 65 years old) receiving anti-TNFα drugs.[50] Drug withdrawal rates and mean Disease Activity Score (DAS28) score changes were similar in both groups at the end of the second year. However, despite clinical responses, improvement in HAQ scores was significantly less in patients with EORA. TNF inhibitors were slightly less or equally effective in reducing disease activity in elderly individuals compared with younger individuals. HAQ scores improved less in patients with EORA, especially in patients aged over 75 years. Randomized controlled trials (RCTs) showed the efficacy of TNF inhibitors (etanercept, infliximab or adalimumab) in elderly patients with early RA who were diagnosed with EORA (Table 2).[51] Evidence for the effectiveness of tocilizumab, abatacept, rituximab and tofacitinib in elderly patients with RA is scarce. Tocilizumab was less effective in the elderly group, and the drug retention rate and discontinuation rates because of adverse events were similar between the two age groups.[52] Data on abatacept in elderly patients with RA have not been published yet. RCTs showed tofacitinib to be similarly efficacious in both groups.[53]

In conclusion, compared with YORA, it was found that EORA had different characteristics (Table 3). EORA is characterized by more equal distribution of sex, higher frequency of acute onset with constitutional symptoms, more frequent involvement of large joints, and lower frequency of RF positivity. Earlier diagnosis, less erosive disease and less DMARD usage were reported as distinguishing patients with EORA from those with YORA. The concern of physicians and patients that drug-related side effects may arise is hampering widespread use of DMARDs. Infections that may develop due to the use of DMARDs are more complicated and serious in elderly patients compared with younger patients and this is a concern of many physicians. However, many studies in recent years have shown that DMARD-related toxicity in the

Table 2. Main studies in the literature showing the efficacy and safety of anti-TNFα drugs in patients with EORA compared with patients with YORA.

Following parameters	EORA	YORA	Efficacy	Safety	Study
HAQ score (mean change from baseline) Mean VAS	0.39–0.92 2.54–3.88	0.57–1.0 2.44–3.38	Similar improvement in functional status and pain score	Similar in both groups in safety data	RCTs Shiff *et al.*[54] ($n = 1847$)
ACR20/50/70 (%) HAQ score	70/45/15 0.46	65/39/15 0.42	Improvement in disease activity and functional status in both groups	Rates of SAEs and serious infectious episodes in elderly patients taking etanercept were not increased compared with age-matched controls taking MTX	RCTs Bathon *et al.*[51] ($n = 2402$)
ACR20/50/70 (%)	66/40/17	69/44/20	No differences in response between EORA and YORA	Rate of any infection was not higher in elderly (1.36 events/patient year) compared with younger patients (1.56 events/patient year)	RCTs Fleischmann *et al.*[55] ($n = 1128$)
Mean change in DAS28 from baseline EULAR response rates (good/moderate/poor) Mean change in HAQ from baseline at 6 months/1 year	–0.63 (at 1 year) –0.65 (at 2 years) 7.2%/32%/60.2% –0.07 (0.02), –0.08 (0.02)	–0.59 (at 1 year), –0.58 (at 2 years) 11.2%/37%/51.5% –0.09 (0.01), –0.12 (0.02)	Change in DAS28 similar in both age groups, fewer good responders and more poor responders among the elderly Smaller improvement in HAQ in elderly patients aged >75 years	No difference in the rate of serious infections between both groups treated with anti-TNFα agents Drug discontinuation rates also similar in the two age groups Cancer significantly more frequent in EORA compared with YORA patients (7.1% *versus* 0%, respectively; $p <$ 0.05)	Observational Genevay *et al.*[50] ($n = 1571$)
Mean change in DAS28 from baseline at 1 year EULAR response rates (good/moderate/poor) Mean change (SD) in HAQ from baseline to 1 year	–1.5 19%/48%/32% 0.20 (0.50)	–1.7 28%/39%/33% 0.33 (0.59)	Significantly less improvement in DAS28 and HAQ from baseline to 1 year in EORA compared with YORA	No significant differences in discontinuation rates and adverse events	Observational Radovits *et al.*[56] ($n = 730$)

ACR, American College of Rheumatology; DAS28, Disease Activity Score; EORA, elderly-onset rheumatoid arthritis; EULAR, European League Against Rheumatism; HAQ, Health Assessment Questionnaire; MTX, methotrexate; RCT randomized controlled trial; SAE, serious adverse event; SD, standard deviation; TNF, tumor necrosis factor; VAS, visual analog scale; YORA, young-onset rheumatoid arthritis.

Table 3. Comparison of main characteristics of patients with EORA and YORA.

Characteristics	EORA	YORA
Prevalence	2%	0.5–1%
Female/male ratio	2/1	4/1
HLA-DRB1	less significant	more significant
Clinical form	classical RA PMR-like form RS3PE s/m like form	classical RA
Laboratory findings		
RF/ACPA positivity	less frequent	more frequent
Elevated ESR/CRP	more frequent	frequent
Treatment		
CS use	first line, single agent	as combined drug
cDMARD use	less frequent	more frequent
bDMARD use	less frequent	more frequent
Drug side effect	more frequent	less frequent
Comorbidity	more frequent	less frequent
Prognosis	similar	similar

ACPA, anti-cyclic citrulinated peptide antibody; bDMARD, biological disease-modifying antirheumatic drug; cDMARD, conventional disease-modifying antirheumatic drug; CRP, C-reactive protein; CS, corticosteroid; EORA, elderly-onset rheumatoid arthritis; ESR, erythrocyte sedimentation rate; PMR, polymyalgia rheumatic; RF, rheumatoid factor; RS3PE, remitting seronegative synovitis with pitting oedema; YORA, young-onset rheumatoid arthritis.

elderly is low and comparable to younger patients. So, even in patients with EORA, DMARD treatment should be started quickly. Because a substantial number of patients with EORA have comorbidities or health-related problems that preclude them from participating in RCTs, a prospective, multicenter large cohort study is required to evaluate the effectiveness and safety of treatment with biological DMARDs in patients with EORA.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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