REVIEW

Late-onset rheumatoid arthritis (LORA)

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Abstract

The proportion of older adults (>65 years of age) has been on the rise. According to the global estimates, there were 700 million elderly subjects (aged 65+) in 2019. The overall number of elderly is expected to increase 2-fold in the next three decades to reach around 1.5 billion by 2050. Presentation of autoimmune disorders like rheumatoid arthritis (RA) is often misunderstood and misdiagnosed in this population due to varied presentations. Diagnosis is often challenging in elderly due to the common presentations of aches and pain despite various underlying etiologies. The acute onset of polyarthritis in elderly is associated with prominent myalgia, fatigue, low-grade fever, weight loss, and depression. Less often, extraarticular manifestations such as nodules or episcleritis may also be present. It is important to understand the altered mechanisms and presentations of existing diseases in younger adults and their manifestations in elderly. The present review article highlighting the varied presentations of RA in elderly may help clinicians in customizing the treatment modalities to address the associated complications.

Keywords: arthritis, late-onset arthritis, pain, disability

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease characterized by erosive arthritis and systemic organ involvement.[1] It can cause rapid destruction of joints, resulting in severe limitations in the patient's functional capacity including reduction in quality of life, inability to work, financial burden, premature aging, increase in morbidity, and higher risk for mortality.[2] RA affects subjects of all ages and both genders, and increased preponderance has been noted in young women aged 25-45 years. Recent studies have reported RA as the most common inflammatory disease prevalent in elderly subjects. The study titled 'The clinical features of rheumatic infection in the old' by the author Schnell is the first to describe the case of an elderly subject with RA.[3] The physiological and immune system changes seen in the elderly population could be the reason for frequent and differential presentations of inflammatory rheumatologic diseases in this age group. Necessary resources for the current review were gathered based on the search strategy using several keywords and subject headings.

Late-onset rheumatoid arthritis (LORA)

Late-onset rheumatoid arthritis (LORA), also called elderly onset rheumatoid arthritis (EORA), is defined as rheumatoid arthritis with onset after 60 years of age.[4, 5] However, some definitions have retained the age cut-off as >65 years.[6, 7] The prevalence of RA increases with age up to the age of 80 years and is seen in 2% of older adults, and it represents 10-33% of all RA cases.[2,5,7,8] LORA was earlier speculated to be indistinguishable from the classic Young-onset RA (YORA), except for later-onset.[9,10] However, recent literature evidence has shown that there are several distinguishable clinical features between LORA and YORA. Several studies have reported more equal gender distribution for LORA compared to YORA. The women-to-men gender ratio for LORA is 2:1 as opposed to 4:1 ratio for YORA. The number of cases of LORA is likely to increase in the coming years with increase in prevalence of elderly over 65 years age in the general population.

It is challenging and tricky to delineate LORA from YORA and also other arthritides that are prevalent in older adults. The long-term consequences such as physical and work disability, reduced quality of life, and premature mortality pose substantial burdens to the healthcare system and society.

Pathobiology

Genetics

The cause of RA is believed to be multifactorial with both genetic and environmental factors playing vital roles. Over

100 risk loci associated with RA have been identified, but the strongest predisposition lies within the *DRB1* locus in the *HLA class 2* gene. Within the *HLA-DRB1* region, a shared sequence of amino acids at positions 70 to 74, termed as 'shared epitope', has been identified as a risk factor for RA.[11] Other susceptible genes include *PTPN22, STAT4, TRF1-C5, PAD14,* and *CTLA4*. RA-associated *DRB1* alleles have shown differences in early and late-onset RA, as well as ethnic variants. A Spain-based study has reported the association of YORA with *DRB1*04*, and LORA with *DRB1*01*.[12] In addition, an increased DRB1*13/*14 association has been noted for seronegative LORA.[12] Kim and colleagues have studied the impact of presence of HLA-DRB1 and HLA-DQB1 genes on susceptibility and disease severity in LORA and YORA patients.[13] The researchers noted that the common epitope was less frequently detected in LORA compared to YORA (49.2% vs. 66.1%).

Pathogenesis of LORA

Aging is a physiological process characterized by reduced T cell proliferation and antibody production to vaccination, and elevated proinflammatory cytokine levels.[14] T cell phenotype alteration, apoptosis defects, cytokine imbalance, and inadequate antigen presentation with an increased reaction to autoantigens have been noted in the immunological response of aged subjects.[8] These physiological alterations make the elderly more prone to infections, autoimmune diseases, and malignancies. Straub et al. have noted that elevated interleukin (IL)-6 secretion is negatively correlated with dehydroepiandrosterone and androstenedione synthesis in patients with LORA.[15] The acute onset and increased acute phase reactants seen in LORA may be explained by the increased IL-6 levels. Punzi and colleagues showed elevated IL-6 levels in the synovial fluid of subjects with LORA as compared to patients with YORA; however, no significant differences were seen in IL-1 and IL-8 levels.[16] Tumor necrosis factor alpha (TNFα) and IL-1 are the two main cytokines that propagate the proliferation of the synovium and increase the secretion of matrix metalloproteinases and adhesion molecules. These immune responses result in synovitis, disabling pain, and swelling, predominantly in the upper limbs in LORA.[2] Increase in the levels of autoantibodies has been found in elderly, hence using rheumatoid factor for the diagnosis of RA is less specific in the elderly and may not correlate with disease severity.[2,17]

Clinical features

LORA can present with overlapping symptoms in three clinical forms and the diagnosis is often challenging. The classical presentation (70%) is the involvement of polyarticular small joint erosions with RA factor positivity. The second form is the polymyalgia rheumatica (PMR)- like presentation with proximal limb involvement and RA factor negativity. Around 25% of patients with PMR can also have asymmetric polyarthritis without joint erosions. The third form is similar to remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome. This is characterized by acute onset of pitting edema in the hand and tenosynovitis with spontaneous remission within 3-18 months. HLAB27 positivity has been noted in these groups of patients.[18] Patients with seropositive LORA have been shown to have more aggressive disease and a worse prognosis, in terms of functional capacity and mortality, as compared to seronegative RA. However, Li et al. observed that the time to remission was similar in both YORA and LORA, with patients on single conventional synthetic disease-modifying drugs (csDMARD) in the latter group.[5]

LORA patients can present with disabling morning stiffness and marked pain predominantly affecting the upper extremities, including systemic symptoms of weight loss, myalgia, and lymphadenopathy.[18] Synovitis of shoulders and wrist joints is a more common presentation in LORA, while the involvement of metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints, elbows, and ankle is more prevalent in YORA. Presence of subcutaneous nodules is less frequent in LORA compared to YORA. LORA is associated with higher Larsen and health assessment questionnaire (HAQ) scores. Studies have noted that the presence of chronic lung diseases and osteoporosis at baseline is associated with an increase in disease activity and worsening of physical function in patients with LORA.[19,20] Patients with PMR are usually >50 years of age with painful shoulders and hip girdles. Bilateral subacromial bursitis is often noted in patients with PMR and can help to differentiate the disease from LORA. Dramatic improvement in PMR has been noted in patients who received low-dose steroid treatment.[21]

Characteristic features that help in differentiating LORA, PMR, and RS3PE are listed in table 1.

Other differential diagnoses to be considered for LORA

Gouty arthritis is caused due to the deposition of monosodium urate crystals in the soft tissues around the joints, including the tendons, cartilages, and synovium. Gout causes intermittent and self-limiting arthritis and it usually involves the metatarsophalangeal (MTP) joint. In certain

Table 1: Characteristics that help in differentiating LORA, PMR, and RS3PE

Characteristics	LORA	PMR	RS3PE
Onset (years)	≥65	>60	>60
Male:female ratio	F=M	F>M	M>F
Involvement of small joints	Mild-prominent	Mild	Mild
Pitting edema	Unusual	None	Prominent
Pelvic girdle stiffness	Rare	None	Less
Anti-CPP antibody	frequent	Less frequent	none
Association with HLA	*HLA-DRB1, DR4*	*HLD DR4*	*HLA B27, A2*
Radiological erosions	Yes	No	No
Synovitis on MRI or USG	Marked	Uncommon-mild	Uncommon-mild, marked tenosynovitis of both flexor and ex-tensor tendons
Response to low-dose steroids	Good	Good	Very good

cases, it can present with polyarticular involvement.[18] Imaging in gouty arthritis shows erosion with sclerotic margins that are remote from the joint, whereas LORA shows periarticular osteopenia with marginal erosions.[18] Thiazides are used as antihypertensives and the elderly may be prone to hyperuricemia. Hence, such patients need close monitoring. Acute gouty arthritis may also present with low serum uric acid levels. However, this is not a contraindication to use thiazides, since elevated blood pressure may increase the risk for cardiovascular disease or strokes.[22]

Osteoarthritis (OA) is a degenerative and destructive disease that commonly involves carpometacarpal joints, distal and proximal interphalangeal joints, and knee joints. There is cartilage degeneration, subchondral bone thickening, and osteophyte formation. Bony hypertrophy in distal interphalangeal joints (Heberden's nodes) and proximal interphalangeal joints (Bouchard's nodes) may be seen on clinical examination. OA is not accompanied by systemic symptoms and MCP joint involvement. Radiologically finding is characterized by osteophyte joint narrowing and subchondral sclerosis.[18, 23]

Calcium pyrophosphate deposition disease (CPPD) is associated with calcium pyrophosphate dihydrate crystal deposition in the articular structures. It commonly presents as chondrocalcinosis with calcification of articular cartilage. Shedding of these crystals into the synovial fluid causes an inflammatory reaction, which presents as a self-limiting acute arthritic attack persisting for one day to four weeks. The most commonly affected joints are the knees and wrists with negative serological tests.[18]

Psoriatic arthritis usually has multi-domain involvement, which includes peripheral joints, and the axial skeleton with or without skin involvement. Characteristic nail changes like onycholysis and pitting are also noted. It may occur as oligoarticular/polyarticular with the involvement of distal interphalangeal (DIP) joints, spondyloarthritis involving sacroiliitis and spondylitis, distal arthritis with the involvement of DIP, and arthritis mutilans. A small number of affected patients may show RF or anti-CCP-positivity.[24]

Reactive arthritis usually presents as asymmetric oligoarthritis of lower limbs including knees, enthesitis, sausage digits (dactylitis), and sacroiliitis. Other features can be anterior uveitis, urethritis and skin involvement. Affected patients may have a history of antecedent infectious illness like genitourinary symptoms or dysenteric illness. HLA-B27 positivity occurs more commonly in reactive arthritis than LORA.[25,26]

Carcinomatous polyarthritis is a seronegative inflammatory arthritis and may be the first sign of an existent malignancy. The possible etiology includes immune mechanisms involving hormones, cytokines, peptides, antibodies, and cytotoxic lymphocytes. Carcinomatous polyarthritis is often associated with lung, colon, ovarian, gastric, oropharyngeal and esophageal tumors, and lymphoproliferative diseases.[27,29] The symptoms usually appear 8 to 12 months

before the development of tumor disease.[27]

Advanced age initiation, acute onset, predominant asymmetrical lower extremity involvement, and sparing of the wrist and hand joints are the characteristic features that differentiate carcinomatous polyarthritis from RA. Erosions, deformities, rheumatoid factor, rheumatoid nodules, and family history are absent in carcinomatous polyarthritis.[30] Symptoms of carcinomatous polyarthritis do not respond to conventional anti-rheumatic treatment and it is imperative to treat the underlying malignancy.

Diagnosis

The diagnosis of LORA needs both clinical and laboratory correlations, since the spectrum of inflammatory arthritis varies from seropositive rheumatoid arthritis to seronegative arthritis. There are overlapping symptoms of PMR with other differential diagnoses not excluding psoriatic arthritis, crystal arthritis, extra-articular manifestations of inflammatory bowel diseases, reactive arthritis, spondyloarthritis, and arthritis as paraneoplastic manifestations.

Laboratory tests

LORA usually reflects a highly active inflammatory status with a raised erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and alpha 2 globulins, and decreased hemoglobin as compared to YORA. The prevalence of both organ and non-organ-specific autoantibodies including RF increases with advancing age. About 56-65% of EORA cases have shown positive rheumatoid factor.[31] RF positivity (nonspecific and usually low titer) is seen in 10% of healthy elderly. Hence, this test has limited diagnostic value in older subjects, and it is recommended to consider the first positive RF titer of 1:1280 in latex fixation test for elderly, as compared to 1:160 in middle age. The anti-cyclic citrullinated antibody (ACCP) that reacts with a common epitope identified by anti-filaggrin, antiperinuclear, and antikeratin antibodies is probably more specific among the elderly, and about a third with seronegative RA presents with ACCP positivity.[32,33] Nearly 65% of the LORA patients has anti-CCP positivity.[34] Compared to YORA, higher IL-6 and lower levels of TNF alpha have been observed in patients with EORA. [35]

Imaging

Conventional radiography is highly specific, although not equally sensitive for detecting joint erosions. Ultrasonography (US) and magnetic resonance imaging (MRI) may reveal erosions, but in EORA, the value of MRI-and US-visualized erosions remains to be validated. MRI and US have been proposed to differentiate EORA from PMR, which is characterized by shoulder bursitis.[18, 36]

Treatment

The treatment of LORA involves treat-to-target (T2T) strategy, where the medications are optimized to achieve the therapeutic goals of pain management, reduction of inflammation, and disease modification, including delaying the progression of the disease and improving functional status as part of recovery and reduce the side effects of medications.[37] Hepatic and renal clearance reduces with advancement in age, and there is a higher tendency for drug interaction and adverse effects.[38] Increase in polymorbid conditions, infections, cardiovascular risks, and malignancies has also been noted with aging. The older adults are prone to polypharmacy, an increase in over-the-counter medications with its added risks. Most clinical trials generally excluded older adults in clinical trials and if included, the numbers are very meager. Due to the lack of clinical data, it is difficult to implement evidence-based modification in prescription practices.

Advancements in medical science have contributed to improved therapeutic options for the management of EORA. The key treatment options for LORA include csDMARDs like methotrexate (MTX), sulphasalazine (SSZ), leflunomide, anti-malarials, biologic agents targeting cytokines including TNFα inhibitors like infliximab (IFX), adalimumab (ADA), tocilizumab (TCZ), etanercept (ETN), anakinra (IL-1 antagonist) and JAK inhibitors (e.g., tofacitinib), and bridging strategies using short-term steroids.[39]

Chronic use of low-dose steroids in RA

Currently, corticosteroids are mainly used in early and established RA as a bridging therapy to DMARDs and during disease flares. Several studies focusing on the use of long-term low-dose glucocorticoids use in the management of RA are currently underway.

A study titled 'Glucocorticoids in rheumatoid arthritis: current status and future studies' reviewed the recent literature data on glucocorticoids use in RA and found that most studies have evaluated glucocorticoid efficacy as bridging therapy, combined with csDMARDs. Studies have mainly focused on patients with early RA, and data on established RA are scarce.[40]

The GLORIA TRIAL, published in 2022, was a pragmatic randomized, double-blinded placebo controlled study that investigated the use of low-dose, add-on prednisolone (5mg/day) in patients with RA aged 65+ years. The study

observed that add-on low-dose prednisolone had beneficial long-term effects in senior patients with established RA, with a trade-off of 24% increase in non-severe adverse effects, suggesting a favorable balance of benefit and harm.[41]

Methotrexate

Methotrexate (MTX) being an antimetabolite, acts by competitively blocking dihydrofolate reductase, thereby inhibiting purine and pyrimidine synthesis required for DNA synthesis. The drug was initially found effective in patients with psoriatic arthritis and became the first-line agent for the treatment of RA, since 1990.[42] Initiating low-dose methotrexate (MTX) is one of the currently used strategies for treating LORA and has been found to be well tolerated.[43] About 30-60% of MTX is protein bound, and a small portion (10%) is monohydroxylated in the liver, which in turn is polyglutamated to MTX glutamates. MTX glutamate has a long half-life of 1 week. Nearly 50-80% of MTX is eliminated via the kidney and 10-30% through bile. Meta-analysis of 11 MTX clinical trials, which comprised 496 RA patients, showed that age did not affect MTX efficacy on tender inflamed joint numbers, ESR, and pain. The study also found that renal function rather than age determined MTX toxicity. 44 Patients with LORA are more likely to be on a single csDMARDs, without biologic or JAK inhibitor.[5]

Sulphasalazine (SSZ)

SSZ is a combination of sulfapyridine and 5-aminosalicylic acid (5-ASA) linked by an azo bond. Sulfapyridine is the active agent in RA and several studies have shown that the onset of response is rapid in SSZ compared to gold or HCQs, and SSZ slows the progression of joint erosion in RA patients. Sulfapyridine is metabolized in the liver via acetylation and hydroxylation.[45] These metabolites are then excreted through urine. The rate of acetylation of sulfapyridine is genetically determined and classified as fast and slow acetylators. Slow acetylators can have a longer sulfapyridine half-life leading to toxicity.[46] The risk for sulpha allergy is found to be higher among those who tested positive for antinuclear antibody (ANA) and anti-Sjogren's syndrome antibody (SSA).[47]

Leflunomide

Leflunomide is an N-(4-trifluoromethyphenyl)-5-methylisoxazole-4-carboxamine and isoxazole derivative. It is absorbed and rapidly converted to active metabolite M1 derivative, which inhibits *de novo* pyrimidine synthesis. Two third of M1 metabolite is excreted through feces and urine. There is a lack of specific pharmacokinetic and pharmacodynamic studies in elderly. No studies have specifically evaluated leflunomide toxicities in elderly RA patients. Chan et al. have reported 18 cases of pancytopenia associated with leflunomide use with a median age of 65.5 years. The authors noted that the risk of pancytopenia increased with concomitant use of MTX in elderly.[48] A retrospective study conducted to evaluate the safety and adherence of leflunomide in the elderly patient with RA or psoriatic arthritis showed that leflunomide was a useful and well-tolerated DMARD for the treatment of RA and psoriatic arthritis in the elderly.[49]

Anti-malarials

Hydroxychloroquine (HCQ) and chloroquine (CQ) are the antimalarials used in the treatment of RA and several studies have proven their tolerability. Nearly 45% of HCQs is excreted renally, therefore patients who are elderly with declining renal function require close monitoring. They are used more predominantly in EORA than YORA.[50] Patients receiving these drugs are advised to undergo regular annual retinal check-up for monitoring HCQ toxicity, though the incidence is <2% upon receiving a dose of 4-5mg/kg/day for <5 years and can increase to almost 20% with 20 years of regular use. A baseline ECG may be needed to check for QT prolongation, especially in those with risk factors like renal failure, cardiovascular diseases, or those on medications that can prolong QT interval.

Biologic agents

These are the newest class of DMARDS that target specific immune components such as upregulated cytokines. The commonly used biologics are TNF inhibitors (infliximab, adalimumab,etanercept) and IL-1 inhibitor (Anakinra). There are insufficient data on the effects of biological DMARDs in elderly. A recent study by Murota et al. has investigated the safety of biologics agents in older patients with RA.[51] The study has revealed age >65 years was independently associated with risk for adverse events leading to discontinuation of biologic agents. Whereas no significant difference was found for the age groups 65-74 and ≥ 75 years, suggesting the need for administering biologic agents with caution.[51]. Kawashima et al. retrospectively analyzed the incidence rate of serious infections that required hospitalization between biologics- and non-biologics DMARD-treated elderly RA patients (>65 years). The researchers have identified the incidence rate to be comparable between the groups. However, patients who received lower doses of prednisolone doses (1-4 mg/day) along with biologics demonstrated increased risk for serious infections.[52] Differences in demographic and clinical features between YORA and LORA are listed in table 2.

Table 2: Differences in demographic and clinical features between YORA and LORA

Features	YORA	LORA
Age of onset of RA	25-45 years	>60 years
Gender distribution, female-to-male ratio	4:1	2:1
Association with HLA DRB1-shared epitope	More frequent (66.1%)	Less frequent (49.2%)
Clinical presentation	Chronic erosive arthritis involving predominantly small joints of hands	Can present with acute disabling morning stiffness and marked pain predominantly affecting upper extremities, including systemic symptoms of weight loss, myalgia, and lymphadenopathy
Synovitis	Synovitis of metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joint, elbows, and ankle are more common in YORA	Synovitis of shoulders and wrist joints is more in LORA
Inflammatory markers, ESR, CRP, and alpha-2 globulin	Relatively less active inflammatory status compared to LORA	Highly active inflammatory status
Prognosis	Fair	Good
Remission	Yes, with DMARDs (less than LORA)	Yes, with DMARDs

Conclusion

In conclusion, it is important to differentiate LORA from other inflammatory arthritides based on clinical symptoms/signs, and serological tests like anti-cyclic citrullinated peptide (CCP) antibodies and musculoskeletal ultrasonography. LORA may present with constitutional features, lower RA positivity, and less erosive disease than YORA. It is vital that aches and pains and general constitutional symptoms should not be castigated as ageing issues, thereby delaying the process of investigation.

The main line of treatment is csDMARDS, biologics, and JAK inhibitors. There is increasing apprehension among physicians to use csDMARDS and biologics in older adults due to their side effects profile. However, this can be reduced by appropriate clinical and correlative diagnostic strategies, wherein treatment options chosen would reduce the risk for toxicity and polypharmacy in the elderly, and still control the inflammatory process and stabilize the disease condition.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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