RESEARCH

A SPIRAL OF CUMULATIVE PROBLEMS: GERONTORHEUMATOLOGY

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Abstract

Gerontorheumatology is an evolving area of medicine. The most common rheumatic diseases in elderly are osteoarthritis, polymyalgia rheumatica, crystal arthropathies and rheumatoid arthritis. Autoimmune and inflammatory rheumatic diseases in elderly have some distinct features when compared to younger adults. Over the past decade, rapid accumulation of data has increased our understanding regarding the mechanisms underlying these distinct features of rheumatic diseases in older individuals. The present article aimed to present common rheumatic diseases in elderly, to review the differences in terms the onset/course of rheumatic diseases between elderly and young adults, and to provide an insight regarding the pathophysiological mechanisms of distinct rheumatic disease patterns in elderly population. In elderly, the presentation at onset and the course of autoimmune inflammatory rheumatic diseases differ from those in younger counterparts. The progressive accumulation of damage at the molecular level triggered by free radicals and spontaneous errors in biochemical pathways stand as the contributors of inflamm-aging. Besides, biomechanical factors and concomitant systemic conditions in elderly can accelerate the progression of rheumatic diseases. In this regard, diagnosis and management of rheumatic conditions in elderly are often challenging and require a comprehensive look.

Key Words: Geriatrics; Rheumatology; Rheumatic Diseases; Signs and Symptoms.

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INTRODUCTION

Ageing involves the progressive accumulation of damage at the molecular level triggered by environmental and metabolically generated free radicals, by spontaneous errors in biochemical pathways, and by nutritional factors (1). Changes occurring in the human body in conjunction with the ageing process includes but not limited to gradual failure in glomerular filtration rate and hepatic oxidative metabolism, increase in proportion of body fat, and decrease in muscle mass (2). And during the process of ageing, individuals become unprotected against diseases such as rheumatologic conditions. Maintaining wellbeing and quality of life in an ageing population is often accompanied by not only significant medical, but social and economic challenges, as well (3).

During the last couple of decades, gerontorheumatology has appeared as an emerging field of medicine. Geriatric rheumatology involves a wide range of autoimmune, inflammatory and non-inflammatory rheumatic conditions/comorbidities in the elderly population (4). Disorders in the era of gerontorheumatology are associated with pain, impairment in mobility, increased risk of falls/fractures, challenges in performing daily living activities and increased morbidity/mortality (5).

Appropriate diagnosis and treatment strategy for these rheumatic diseases require a comprehensive look. It is of utmost importance to recognize the symptoms/signs which are compatible with the common rheumatic conditions in elderly. It is also essential to be aware of the differences in clinical presentation of the elderly individuals with certain rheumatic diseases (i.e rheumatoid arthritis) when compared to younger adults with similar conditions. On the other hand, tailoring appropriate treatment strategies along with a multi-disciplinary approach is of necessity. Non-pharmacological treatment options such as electrotherapy are widely used in chronic rheumatic conditions. It is of great benefit to implement non-pharmacological strategies into management plan in elderly (6). Otherwise, pharmacological approaches/interventional treatments should be tailored with much attention to this particular risk population (5).

The present article aimed i) to introduce common rheumatic diseases in elderly, ii) to discuss the differences in terms the onset/course of rheumatic diseases between elderly and young individuals, iii) to provide an insight regarding the potential underlying mechanisms distinct rheumatic disease patterns in elderly.

Common rheumatic diseases in elderly

Advancements in prompt diagnosis and accurate management strategies have led an increase in the mean age of the population worldwide (7). Compatible with this fact, in the meanwhile, geriatric conditions stand as an important health-care issue. Musculoskeletal diseases are among the most common health-related conditions in the elderly population. The most frequently observed rheumatic conditions are osteoarthritis, polymyalgia rheumatica, crystal arthropathies and elderly-onset rheumatoid arthritis. However, the list can be extended by further adding other autoimmune inflammatory and non-inflammatory rheumatic conditions.

The frequency of musculoskeletal conditions and related health-care demand tend to increase by age. In an elderly individual with a rheumatic disease, continuing loss of neuromuscular performance, chronic pain and loss of mobility further deteriorates the disease course (5). This vicious cycle interferes with the psychological well-being, ability to socialize and overall, the quality of life. The present review will discuss common rheumatic conditions in elderly, particularly by focusing on the distinct features of disease presentations, pitfalls in diagnosis and challenges in management/treatment.

Osteoarthritis

An ageing body is subject to numerous changes occurring in every organ and system. Joints are one

of the most frequently effected components of the musculoskeletal system. Degeneration is an inevitable consequence for the joints bearing the body's weight (knees, hips) or for those exposing to repetitive trauma (hand joints) throughout the life-time. Thus, osteoarthritis is the most common joint disease in elderly population. The frequency rates are higher in females and those aged 80 and above (7).

There are several factors underlying the degenerative changes in elderly. The multi-causation disease model of osteoarthritis is related to both biochemical and biomechanical factors (8). Joint degeneration is a consequence of ageing. Over years of time, misalignment in the adjacent joints (hip, ankle, foot) may alter load distribution and cartilage homeostasis leading to a degenerative state in the knee joint (9, 10). Lifestyle factors (dietary habits, physical activity, etc.) are also important for the development of osteoarthritis in elderly (11). On the other hand, isolated patellofemoral osteoarthritis was not found to be associated with demographic variables in elderly, suggesting a distinct pathophysiological pattern (12). Park et al. found that low education level, low income, rural residence and having no spouse were significantly related to osteoarthritis-related morbidity (7). Comorbidities in elderly such as metabolic syndrome or diabetes may also contribute to the development/progression of osteoarthritis either by increasing inflammation or through the potential joint-toxic effects of glycation end-products. Osteoarthritis has also been associated with frailty, pre-frailty and cardiovascular disease particularly among patients with multi-joint involvement (13-15). Osteoarthritis is now considered as a rheumatic condition involving low-grade inflammation. Dysregulation/inefficiency of the immune system in an aging human accelerates this inflammatory process (16).

While managing an elderly patient with osteoarthritis, several issues should be considered meticulously. In terms of imaging, plain radiographs are recommended at first line to avoid unnecessary magnetic resonance imaging (MRI) (17). On the other hand, certain MRI findings (meniscal damage) may be considered as a part of normal aging. However, cartilage defects, bone marrow edema and synovitis are major contributors of osteoarthritis progression (18). Treatment of osteoarthritis in elderly should be individualized, patient-centered and based mostly on non-pharmacological strategies (19).

Polymyalgia rheumatica

Polymyalgia rheumatica is a common inflammatory rheumatic disease in people aged over 50 years with a peak incidence occurring at age 70-75 years. It can occur as an independent condition or in conjunction with giant cell arteritis. The disease is characterized by pain in the proximal girdles. Patients may also experience malaise, stiffness, arthritis, fever and loss of weight. Aberrant immunologic response of T cells, imbalance in B cells and the Janus kinase (JAK)/signal transducer of activation pathway may underlie the disease pathophysiology (20, 21).

Ruling out other conditions that may mimic polymyalgia rheumatica is crucial in an elderly individual. These include but not limited to malignancies, inflammatory/metabolic myopathies, chronic infections, endocrinopathies/metabolic bone diseases and chronic pain syndromes (21). The hospitalization of the elderly would be beneficial when there are signs suspicious of a paraneoplastic syndrome. Lack of response to glucocorticoids should be considered as a strong warning in this direction (22).

In elderly, comorbidities and issues related drug safety may affect treat to target considerations. Low-to-medium dose glucocorticoids are the cornerstone of treatment, methotrexate provides modest benefits and there are promising reports regarding tocilizumab monotherapy (23, 24). On the other hand, glucocorticoid-based regimens cause much of the morbidity related to polymyalgia rheumatica in elderly (21). Therefore, glucocorticoids should be used at minimum effective dose for a minimum

possible duration and drug-related adverse events should be monitored very closely (25).

Crystal arthropathies

The frequency of clinically manifest gout is above 7% among individuals aged over 65 years (26). By aging, the production of interleukin (IL)-1β by monocytes as a response to the stimulation with monosodium urate crystals shows significant increase. As a result, elderly patients are more likely to exhibit strong inflammatory responses during gout attacks (27). In contrast to young individuals, polyarticular manifestations, atypical presentation (i.e. involvement of ankles and wrists), systemic upset and tophi are common in elderly patients with crystal arthritis (28, 29). The frequency of fever during an attack is 51.1%, 20.8% and 30.8% in elderly, young and middle-aged patients, respectively. Acute phase response is also higher when compared to younger adults. In this regard, clinical picture of crystal arthropathies in elderly may resemble infectious and other inflammatory arthritis (27). Crystal arthropathies are associated with several conditions/diseases in elderly. Patients should be closely monitored in terms of nephropathy and cardiovascular complications. Gout is found to be significantly associated with a higher hazard of incident myocardial infarction in elderly (30).

Non-pharmacological measures (i.e. diet and lifestyle changes) are essential for the management of crystal arthropathies. In elderly, pharmacological treatment should be directed by taking individual risk profile into consideration. Colchicine may lead to gastrointestinal side effects at high doses. Non-steroidal anti-inflammatory drugs should be avoided in patients with renal insufficiency. The use of allopurinol is also restricted in case of renal failure. Febuxostat stands as an alternative for patients intolerable to allopurinol. Evidence regarding the effectiveness and safety of biological drugs and synthetic uricases in elderly patients with gout are still sparse (31).

Elderly rheumatoid arthritis

Elderly rheumatoid arthritis is classified into younger-onset elderly rheumatoid arthritis and elderly-onset rheumatoid arthritis (EORA). Commonly accepted definition for EORA includes the onset of rheumatoid arthritis after 60 years of age, however this definition is subject to modification/validation in future. As the life expectancy has been increasing in the general population, the frequency of EORA is also expected to increase over the next decades (32).

There are several distinct features of EORA when compared to younger-onset elderly rheumatoid arthritis and early-onset rheumatoid arthritis (33). Studies from different geographical areas and on distinct ethnic populations indicate that the prevalence and incidence rates of EORA are higher than early-onset rheumatoid arthritis. According to a study by Rasch et al., the prevalence of rheumatoid arthritis in people 60 years of age and older is approximately 2% (34). A study by Carbonell et al. revealed that estimated annual incidence rate of rheumatoid arthritis among men and women aged 61-70 years is 9.1/100,000 and 14.5/100,000, respectively (35). It is also notable that above the age of 70 years, the incidence rates showed an increase and sex discrepancy disappeared; 15.8/100,000 and 15.3/100,000, in men and women, respectively (35). Thus, EORA is characterized by more equal sex distribution when compared to younger-onset elderly rheumatoid arthritis. Alleles encoding the shared epitope were less commonly identified in EORA than the younger-onset elderly rheumatoid arthritis. Human leukocyte antigen (HLA)-DRB1*04-related alleles were not closely related to EORA and HLA-DQ*04 alleles are also less significant in EORA susceptibility (36, 37).

In terms of clinical picture, acute onset with accompanying constitutional symptoms (weight loss, lymphadenopathy, myalgia, etc.) is more likely in EORA when compared to younger-onset rheumatoid arthritis (38). Although polyarthritis involving

small joints as seen in classical rheumatoid arthritis is the most common clinical presentation, EORA can also present with predominant large joint manifestations (33). While the former is characterized by higher rates of rheumatoid factor (RF) positivity and joint erosions, the latter may have a pattern resembling polymyalgia rheumatica with proximal joint involvement, hip and shoulder girdle pain, seronegativity and higher erythrocyte sedimentation rate (39). Another potential clinical presentation is characterized by wrist tenosynovitis, pitting edema in hands, which is similar to remitting seronegative symmetrical synovitis with pitting edema (RS3PE) (33).

The type of manifestation at initial onset appears as an important predictor of accurate diagnosis, treatment decision and disease progression. Patients with signs/symptoms similar to classical rheumatoid arthritis are more likely to show hand/wrist bony erosions, rapid progression of the disease and impairment in hand functions (39). While managing these patients, potential underlying malignant condition should be always kept in mind. Therefore, diagnostic procedures should focus ruling out paraneoplastic arthritis. In case of a certain diagnosis of EORA presenting as the classical rheumatoid arthritis with seropositivity, disease modifying antirheumatic drugs (DMARDs) should be tailored meticulously. EORA presenting with large joint (i.e. knee joint) monoarthritis at initial onset is characterized by less erosive arthritis and requires less use of DMARDs. However, given its distinct features such as seronegativity, it can be more challenging and time-consuming for physicians to come up with a certain diagnosis. Other potential causes of monoarthritis such as septic arthritis, flare-up of osteoarthritis, crystal arthropathy, traumatic arthritis and paraneoplastic arthritis should be ruled out. In case of proximal joint involvement at initial onset, excluding polymyalgia rheumatica is necessary. Synovial and extrasynovial shoulder lesions may differ between polymyalgia rheumatica and EORA. Polymyalgia rheumatica is more likely to present with inflammation in extrasynovial soft tissues compared with EORA. On the other hand, tenosynovitis of the long head of the biceps or glenohumeral joint synovitis are more common in EORA (40). In terms of bursal lesions, semi-quantitative scores for subacromial, subthoracoid and subdeltoid bursae were found to be higher in patients with polymyalgia rheumatica-like onset EORA than in actual polymyalgia rheumatica (41). Takahaski et al. evaluated the differences in fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) uptake patterns between patients with EORA and polymyalgia rheumatica (42). Patients with EORA revealed circular and linear uptake patterns around the humeral head. Patients with polymyalgia rheumatica showed focal uptake in front of the hip joint, indicating iliopectineal bursitis. The authors observed high sensitivity (92.6%) and specificity (90%) for polymyalgia rheumatica diagnosis when a patient meets 3 or more of following items; FDG uptake in ischial tuberosities and spinal spinous processes, characteristic findings of shoulder and iliopectineal bursitis, and lack of FDG uptake in the wrists (42). Wakura et al. detected abnormal FDG accumulation at the entheses in polymyalgia rheumatica, suggesting FDG-PET/CT as a useful method to differentiate EORA from polymyalgia rheumatica (43). Pitting edema at onset was also proposed as an indicator of good prognosis. This form of EORA resembles RS3PE. Evaluation of intra- and extra-articular lesions by ultrasonography would be beneficial to discriminate EORA form RS3PE. Kawashiri et al. found that severe articular synovial hypertrophy was more frequent in patients with EORA and bone erosion was detected in some EORA cases. Digital flexor tenosynovitis and digital extensor tendon peritendinitis were more common and severe in patients with RS3PE (44).

Overall, prognosis and/or treatment response in EORA depends on several factors. Concomitant diseases pose extra risk for poor prognosis. On the

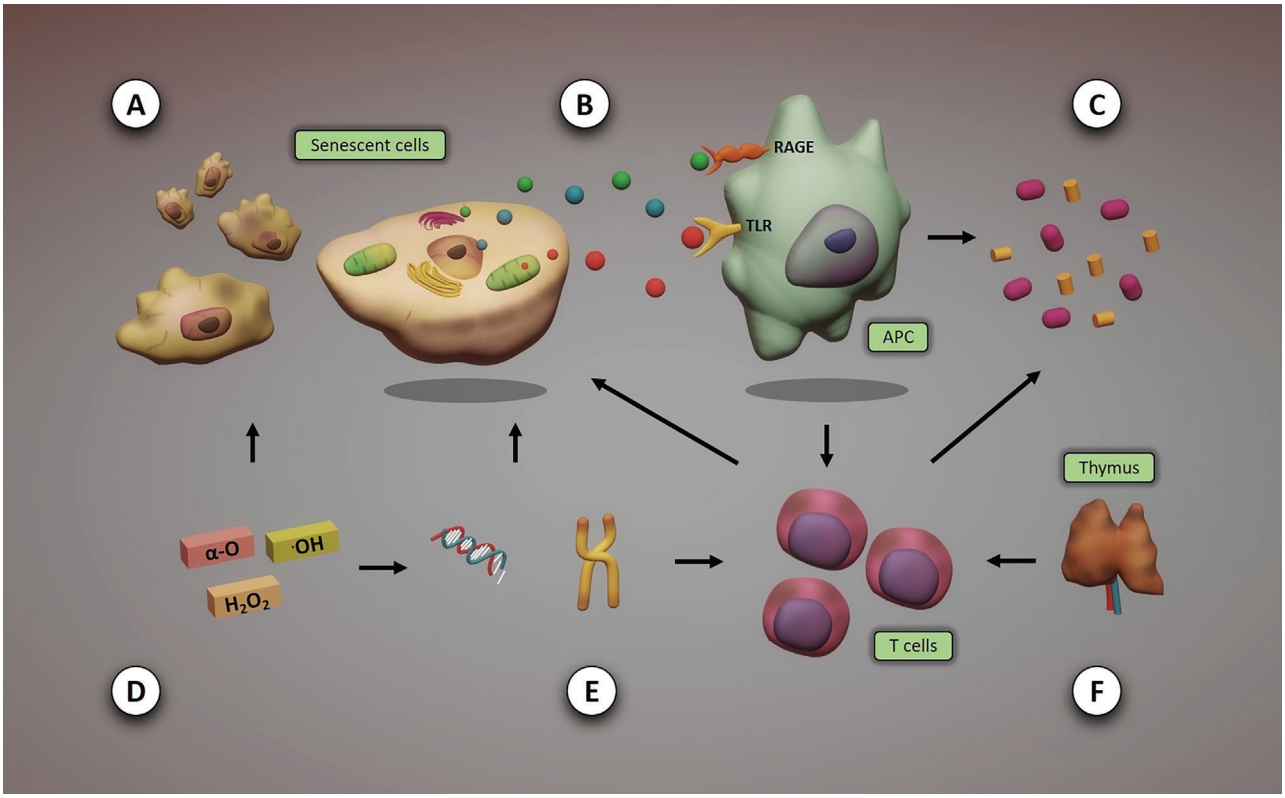
other hand, rheumatoid arthritis itself may also contribute to morbidity such as increased risk of cognitive impairment (45). There may be distinct processes operating at the synovial tissue level, as well. Romao et al. conducted a study among patients with younger-onset rheumatoid arthritis and EORA (46). Patients were undergone ultrasound guided synovial biopsy prior to conventional immunosuppressive treatment and after 6 months of therapy. Patients with EORA were more frequently male, had more comorbid conditions, proximal joint involvement, weight-loss and extra-articular features. The proportion of individuals with low disease activity at 3 and 6 months were similar between two groups. However, patients with EORA experienced significantly higher ultrasound-based synovitis score at 6 months. Baseline disease activity score and smoking habit were appeared as the predictors of poor treatment response. On the other hand, polymyalgia-like onset was associated with favorable clinical outcome. In terms of histological parameters, patients with EORA presented only mild improvement in synovitis, sublining macrophage, and T cell scores, with no significant changes in lining macrophages, B cells and plasma cells (46). As a result, prognosis in EORA depends on numerous factors including initial presentation, seropositivty, lifestyle factors and comorbidities.

The potential underlying mechanisms of distinct rheumatic disease patterns in elderly

In elderly, the frequency, the initial presentation and the progression of rheumatic diseases may differ from those in young adults (47). The distinct features of rheumatic diseases in elderly may be related to the discrepancies in hormonal and immunological background including immunosenescence (33, 46). For a proper immune system functioning, the clearance of dead cells is essential. Decreased clearance of apoptotic elements with aging would lead to the accumulation of dead cells, which in turn contributes to accelerated inflammatory response. The debris stands as a possible source of auto-antigens, contributing to the expression of auto-antibodies and autoimmunity (47). On the other hand, decreased autophagy leads to the accumulation of adipokines, reactive oxygen species, and cytokines, increasing systemic inflammation and oxidative stress (48). Other senility-related cellular alterations include T-cell phenotype change, cytokine imbalance, inadequate antigen presentation and deterioration in specific immune response (33). Inflamm-aging is a process used to define this chronic, low-grade inflammatory response to the repetitive antigenic burden with aging (49). Given its multi-factorial process, aging is related to inevitable consequences at the molecular, cellular, tissue and organ level. Aging leads to a senescent-cell phenotype through several changes in cells. These include genomic instability, telomere attrition, epigenetic changes, decreased proteostasis and dysregulation of oxidative stress (16). Senescence-associated secretory phenotype of some certain aging cells is related with increased secretion of pro-inflammatory cytokines/chemokines (i.e. IL-6) (50). Both these pro-inflammatory mediators and increased concentrations of reactive oxygen species/free radicals trigger the release of damage-associated molecular patterns (DAMPs); one of the important determinants of inflamm-aging. DAMPs trigger the intracellular inflammasome and interact with toll-like receptors, as well as the receptor for glycation end products (RAGE). These factors further increase the production of pro-inflammatory mediators (IL-1β, IL-6, IL-18, etc.) and pro-catabolic factors (i.e. matrix metalloproteinases) in an ageing joint (16) (Figure 1).

Other than the dysregulation/decreased efficiency of immune system, aging individuals experience some biomechanical changes, as well. Sarcopenia, changes in alignment and/or specific muscle weaknesses serve as mechanical stressors for joints. For instance, poor quadriceps function may predispose knee osteoarthritis, while hip abductor weakness may increase the risk of gluteal tendinopathy

Figure 1. Contributors of inflammation in elderly. Illustrated by the author ICB. A- Aging leads to a senescent-cell phenotype, B- Senescence-associated secretory phenotype (SASP) is characterized by the increased release of damage-associated molecular patterns (DAMPs). DAMPs bind their receptors [i.e. toll-like receptors (TLR), receptors for glycation end products (RAGE)] on antigen presenting cells (APCs), C- DAMP-receptor interaction causes an increased production of pro-inflammatory cytokines and pro-catabolic factors, D- Age-related dysregulation of reactive oxygen species (ROS) such as hydroxyl radical (·OH), alpha oxygen (**α**-O) and hydrogen peroxide (H_2O_2) contributes to oxidative molecular damage, E- Oxidative stress-related DNA damage and age-related telomer shortening further add to the increase in senescent cells, F- Aging is associated with thymic involution which is followed by the alteration in T cell phenotype and function. This phenomenon leads to an impairment in senescent cell removal and further accelerates the production of pro-inflammatory cytokines and chemokines.



and hip osteoarthritis (5). Besides, comorbidities in elderly such as cardiovascular diseases, chronic kidney disease, neurological conditions contribute to the mechanical confounders through impaired mobility and disuse atrophy.

Conclusions and future perspectives

Common rheumatic diseases in elderly include osteoarthritis, crystal arthropathies, polymyalgia rheumatica and rheumatoid arthritis. Clinical presentation at onset and progression of the rheumatic diseases may be different in older adults. Elderly-onset rheumatoid arthritis may present with monoarthritis and seronegativity is common. On the other hand, crystal arthropathies may present with polyarthritis and systemic manifestations. Rheumatic diseases in elderly may mimic malignancies, chronic infectious diseases, endocrinopathies/metabolic bone diseases and chronic pain syn-

dromes. Hormonal, metabolic, biomechanical and immunological discrepancies are related to the distinct features of rheumatic diseases in elderly. Low-grade inflammatory response to the repetitive antigenic burden with aging is the main driver of inflammatory rheumatic conditions in older adults. Genomic instability, telomere attrition, decreased proteostasis and epigenetic changes lead to a senescent-cell phenotype which induces the secretion of pro-inflammatory cytokines and pro-catabolic factors. Reactive oxygen species further contributes to this inflammatory process named as inflamm-aging. Further studies would increase our understanding regarding the pathophysiology of inflamm-aging which can be regarded as a potential target for the management of inflammatory rheumatic diseases in elderly.

There are surely several challenges regarding the rheumatic diseases in geriatric population, such as: a-Markers of inflammation are higher, b- The prevalence of autoantibodies is increased, c-Diagnostic criteria based on the evidence in younger population may not be accurate in the elderly population, d- Comorbidities, polypharmacy, changes in pharmacokinetics and pharmacodynamics of the drugs should also be taken into consideration. Greater understanding and knowledge seem to allow the translation into better management for elder patients. Fortunately, there has been increasing interest in research on immunologic, physiologic, and psychosocial aspects of aging.

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