
Late-onset rheumatoid arthritis and late-onset spondyloarthritis

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ABSTRACT

Both rheumatoid arthritis and spondyloarthritis may have a late onset. Elderly-onset rheumatoid arthritis is usually defined as rheumatoid arthritis with onset at age 60 or over. It appears to be a heterogeneous disease, with a seropositive subset resembling adult-onset rheumatoid arthritis, and a less severe seronegative subset which sometimes exhibits features overlapping with those of polymyalgia rheumatica. The spondyloarthritis complex includes definite entities as well as undifferentiated forms. Each of these may have a late-onset. Late-onset undifferentiated spondyloarthritis appears to be relatively more frequent than late-onset ankylosing spondylitis. Its clinical spectrum seems to be as broad as that observed in young and middle-aged adults with the exception of distal inflammatory swelling with pitting oedema. A special aspect of the differential diagnosis is the discrimination from other elderly-onset diseases showing the inflammatory swelling with pitting oedema over the dorsum of feet or hands. Psoriatic arthritis frequently begins in the elderly and shows some differences from the younger onset disease. Regarding the management, patients with late-onset rheumatoid arthritis and spondyloarthritis are treated similarly to younger patients taking into account age-related changes in the pharmacokinetics and pharmacodynamics of drugs and the presence of conditions able to reduce medication adherence.

Introduction

Both rheumatoid arthritis (RA) and spondyloarthritis (SpA) may have a late onset. In both, it has been debated whether later age can have an influence on the onset and the evolution of disease.

Elderly-onset rheumatoid arthritis

Definition and clinical manifestations

Elderly-onset RA (EORA) is usually defined as RA with onset at age

60 years or over (1-6), and represents about 10% to 33% (3) of all RA cases. Initially, EORA was considered virtually indistinguishable from classical adult-onset RA except for the later onset (7). However, over time, it has become increasingly clear that EORA differs from classical RA for a number of features. In particular, compared with adult-onset RA, numerous (although not all) studies have reported in EORA a more equal gender distribution (2, 8, 9), more elevated acute-phase reactants (1, 10), and a higher frequency of abrupt onset of symptoms (1, 8, 9, 11, 12), of constitutional manifestations (3, 9), and of a clinical presentation resembling polymyalgia rheumatica (PMR) with prominent shoulder involvement (1, 4, 9, 13). Conversely, erosive joint disease (5), rheumatoid factor positivity (1, 4, 13), and extra-articular manifestations including subcutaneous nodules (1, 4, 13) are less frequent in EORA than in classical RA. Overall, better outcome has been reported in EORA compared with adult-onset RA patients (1, 3, 5), despite the fact that elderly subjects have a decreased functional capacity compared to adults (14). These differences, including the more benign course of EORA, do not appear to be related to a longer disease duration in adult-onset RA compared to EORA, since they have also been documented in studies matching EORA and adult-onset RA patients for disease duration (1, 3). In contrast, there is evidence suggesting that the lesser severity of EORA compared to classical RA is related to a subset of EORA patients (comprising about 50% of all EORA cases) with negative rheumatoid factor running a milder disease course with more benign joint involvement, sometimes resembling that seen in PMR (1, 8). Conversely, patients with seropositive EORA have been shown to have a more aggressive disease and a worse prognosis in terms of functional capacity and mortality (similar to that of

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classical RA) compared with seronegative patients (3, 15).

Therefore, EORA appears to be a heterogeneous disease, with a seropositive subset resembling adult-onset RA, and a less severe seronegative subset which sometimes exhibits features overlapping with those of PMR (1).

Laboratory tests

Laboratory tests in EORA usually reflect the highly active inflammatory status, with raised erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and α_2 globulins and decreased haemoglobin (1, 4, 16).

Rheumatoid factor is positive in about 43% (4) to 48% of cases and identifies a subset of EORA patients with a more aggressive, erosive joint disease. However, it should be noted that non-specific (usually low-titer) rheumatoid factor positivity is found in approximately 10% of healthy elderly subjects (6).

Anti-cyclic citrullinated peptide antibodies (anti-CCP) have been reported in 56-65% of EORA patients (17, 18). A significant correlation between rheumatoid factor and anti-CCP positivity has been documented in one (18), but not in another study (17). Definite proof that anti-CCP antibodies are linked to a worse prognosis in EORA (as they are in classical RA) is still lacking. However, a study linked higher values of anti-CCP to extraarticular manifestations, radiological damage, and disease-modifying antirheumatic drug (DMARD) treatment of EORA (17). In terms of differential diagnosis, identification of anti-CCP is useful for distinguishing seronegative EORA from PMR (8).

Imaging

Conventional radiography is highly specific, although not equally sensitive, for detecting joint erosions. Ultrasonography (US) and magnetic resonance imaging (MRI) (19) may show erosions when plain x-rays are still normal, but the prognostic value of erosions on US and MRI in EORA remains to be validated. US (20) and MRI (21) has also been proposed to distinguish EORA from PMR, which is characterized by shoulder bursitis (22, 23). In this regard, a study demonstrated a significantly

Table I. Diseases that should be considered in the differential diagnosis of elderly-onset rheumatoid arthritis.

a) <i>Inflammatory diseases</i>
• Polymyalgia rheumatica
• Late-onset spondyloarthropathies (psoriatic arthritis, arthritis associated with inflammatory bowel disease, reactive arthritis, undifferentiated spondyloarthropathy)
• Crystal arthritis
• Paraneoplastic arthritis
• Viral arthritis
b) <i>Non-inflammatory diseases involving the shoulder girdle</i>
• Osteoarthritis
• Bilateral rotator cuff tendinitis
• Bilateral frozen shoulder
• Hypothyroidism
• Parkinson's disease

higher frequency of subacromial and subdeltoid bursitis in PMR compared with EORA patients, whereas the frequencies of shoulder joint synovitis and of biceps tenosynovitis were comparable in the two groups (20). In contrast, scintigraphy of shoulder joints has no value in discriminating between EORA and PMR, arguably because synovitis of the shoulder joint is a frequent feature of both EORA and PMR (16).

Differential diagnosis

Detailed differential diagnostic considerations are beyond the scope of this paper, but a list of the principal disorders that may be confused with EORA is reported in Table I. In practice, EORA should be mainly differentiated from PMR and from late-onset SpA.

Prominent synovitis and positive rheumatoid factor, anti-CCP, or both, point away from PMR and to seropositive EORA.

Seronegative EORA and PMR are more difficult to differentiate from each other. Peripheral synovitis is observed in up to one-quarter of PMR patients (24, 25), while about one-sixth of EORA patients report PMR-like manifestations (1, 4, 9, 26), which blurs the boundaries between the two conditions. The difficulty of reliably discriminating seronegative EORA from PMR is emphasized by data showing that up to 20% of EORA patients are initially classified as having PMR (27), while 13% of EORA patients have been reported as having a PMR-like myalgic presentation (26).

Some investigators have hypothesized that seronegative EORA and PMR may be the same entity (28, 29). Indeed, both disorders exhibit not only partially overlapping clinical manifestations, but also similar patterns of HLA-DR associations (25, 30), of T-cell population abnormalities (31), and of a prominent inflammatory response with high circulating IL-6 levels (11, 32). However, the hypothesis that seronegative EORA and PMR are the same disease does not stand to a closer scrutiny based on longer-term clinical observations, which reveal some differences between these conditions. A prospective, 12-month study of 116 consecutive patients presenting with bilateral shoulder pain and a raised ESR showed that peripheral synovitis was more common in patients eventually diagnosed with RA (79% of cases) than in those with a final diagnosis of PMR (26% of cases) (27). Likewise, a recent study comparing seronegative EORA patients (fulfilling the ARA 1987 revised criteria for the classification of RA) with PMR patients (fulfilling the Bird criteria) (33) showed that patients with seronegative EORA had a longer duration of arthritis (over 2 years in 43% of EORA versus 0% of PMR patients). They also showed a more frequent wrist, metacarpo-phalangeal, and proximal interphalangeal joint involvement, and a more frequent erosive course (35% versus 0%) (25). In this latter study, peripheral synovitis was not uncommon in PMR (23% of cases), but PMR-related polyarthritis

occurred mostly at disease onset, was usually associated with myalgia, and responded rapidly to glucocorticoids, while flares or relapses were usually characterized by a highly glucocorticoid-sensitive arthritis.

Treatment

Caution should be exerted in treating EORA patients because of age-related co-morbidities, multiple treatments, and the increased risk of renal, cardiovascular, and gastrointestinal toxicity (6, 8). At the same time, the risks related to drug therapy should be carefully balanced against the expected clinical benefit. With regard to the risks, it is worth bearing in mind that diminished organ function, rather than advanced age *per se*, is a risk factor for drug toxicity (6). This concept is substantiated by numerous studies showing similar DMARD toxicity in young and elderly RA patients with overall preserved organ function (34–37). Therefore, in principle, no medications usually employed for RA therapy in younger subjects should be excluded from the treatment of EORA patients (8). As in classical RA, treatment should ideally be tailored to the individual patient taking into account disease severity and adverse prognostic factors. In particular, since seropositive EORA carries the worse prognosis, an aggressive treatment is often required in this patients' subset. Consistent with this notion, it has been shown that patients with seropositive EORA are usually treated in the same fashion as those with adult-onset RA, while patients with seronegative EORA are less likely to receive DMARD therapy (3, 4).

However, there still seems to be some reluctance to employ biological agents and combined DMARD therapy in EORA resistant to DMARD monotherapy. In this regard, a study showed that EORA patients were less likely than adult-onset RA patients to receive biological or combined DMARD treatment despite identical disease duration and comparable disease activity (38). There are no controlled studies on DMARDs or biological agents in EORA. Low-dose glucocorticoids are often used to treat EORA patients (1, 4,

39). Glucocorticoids have the distinctive advantage over non-steroidal anti-inflammatory drugs of being virtually devoid of gastrointestinal or renal toxicity and may also have disease-modifying properties (40, 41). Chrysotherapy (37) and D-penicillamine (42), despite being as effective and no more toxic in the elderly than in adult patients, have been abandoned in favour of other DMARD with a more advantageous efficacy-toxicity profile. Methotrexate is probably the most popular DMARD. Low-dose (5–7.5 mg weekly) methotrexate has been shown to be effective and safe in elderly patients with RA (36), although it should not be used in patients with severely impaired renal function (creatinine clearance less than 30 ml/min). Hydroxychloroquine and sulfasalazine are acceptable alternatives for mild to moderate disease, while leflunomide may be used in more severe disease (38, 43). As for biological agents, a recent post-hoc analysis of clinical trials demonstrated that etanercept was just slightly less effective in elderly patients, while there was no increased toxicity compared to placebo or methotrexate-treated patients (14).

Late-onset spondyloarthritis

Definition and clinical manifestations

The SpA group includes ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis (ReA), inflammatory bowel disease (IBD) related arthritis, as well as forms that do not meet criteria for these categories, which are designated as undifferentiated SpA (uSpA) (44–47). Each of these may have a late onset (48).

The onset of AS, as defined by the currently used classification criteria, i.e. the New York (49) and the modified New York criteria (50), is uncommon after the age of 50 (51–54). In a population-based descriptive study performed in Rochester, Minnesota, the incidence of AS was 7.3/100.000 per year for all ages and 2.2/100.000 per year after the age of 55 (53). In the recently published survey on a large number of patients of the German Ankylosing Spondylitis Society only 6% had the onset of symptoms after the age of 40 (54). In German patients the frequency of late-onset

disease was significantly higher in the HLA-B27-negative group (55). There seems to be many more similarities than differences between the clinical presentation of late onset and that of classical onset disease. Patients have axial symptoms with or without peripheral arthritis, peripheral enthesitis or dactylitis. Usually, the acute phase reactants are strikingly increased. In a French series of late-onset AS, 70% of the patients were HLA-B27 positive (52).

Late onset of uSpA appears to be relatively more frequent than late-onset AS (56–62). The first study calling attention to late-onset uSpA was published in 1989 (56). Dubost and Sauvezie described the case histories of 10 B27-positive men who, after the age of 50, developed an oligoarthritis together with a large inflammatory pitting oedema of the lower extremities. They had minimal involvement of the axial skeleton, unexplained constitutional symptoms and high levels of ESR. The response to antiinflammatory drugs was poor and symptoms continued from one to several years. Nine patients met the Amor criteria for SpA at diagnosis. Five patients developed sacroiliitis during the follow-up and four of these fulfilled criteria for AS. The authors differentiated their late-onset peripheral SpA from the RS₃PE (remitting, seronegative, symmetrical synovitis with pitting oedema) syndrome reported by McCarty and co-workers (63, 64). Interestingly, 2 out of the 10 patients presented with bilateral shoulder and hip symptoms mimicking PMR. In 1991, Dubost *et al.* reviewed the files of male patients hospitalized over a period of 12 years for rheumatoid factor negative arthritis beginning after the age of 50 (57). Patients with PMR, PsA, or crystal-induced arthritis were excluded. Of the 105 patients, 29 met the ACR criteria for RA, 29 the New York criteria for AS, 3 had ReA and 44 had unclassified arthritis. Of these 44, 14 were B27-positive. Most of these last patients had oligoarthritis together with inflammatory pitting oedema, marked constitutional symptoms and elevated ESR suggesting that late-onset uSpA may occur mostly with this pattern.

With the aim to define the clinical spectrum of uSpA, we studied all con-

secutive patients older than 45 years at the onset of the first symptom of SpA and not meeting criteria for any of the definite categories of SpA seen in a 5-year period (58, 59). Twenty-three patients (11 men and 12 women; 17 B27 positive and 6 negative) were seen in the study period. Of these, 12 had 3 or more clinical manifestations of SpA including peripheral arthritis, peripheral enthesitis, dactylitis, inflammatory spinal pain, buttock pain, chest wall pain, heart involvement, acute anterior uveitis and sacroiliitis. Seven patients showed 2 manifestations and 4 only one. Only 10 of the 23 patients had peripheral arthritis, 3 of whom had ankle or tarsus involvement together with the large inflammatory pitting oedema described by Dubost and Sauvezie (56). Of the two patients with only one manifestation, 1 had peripheral enthesitis and 1 acute anterior uveitis. Of the 23 patients, only 15 met the European Spondylarthropathy Study Group (ESSG) (46) and/or the Amor criteria (45) for SpA suggesting that more sensitive criteria are desirable. The conclusion of the study was that inflammatory pitting oedema is not always present and that the clinical spectrum of uSpA is as broad in the elderly as it is in children and young and middle-aged adults. The differences from the conclusion of the French study depend on the study design. Dubost and coworkers examined retrospectively only male patients with uSpA showing peripheral arthritis (57). On the contrary, we studied prospectively consecutive patients with late-onset uSpA independently of the modalities of onset and sex. Synovitis with pitting oedema has also been observed in patients with longstanding AS (65, 66).

In 1997, Caplanne *et al.* compared the clinical presentation of late-onset SpA with patients with early-onset SpA (60). Eight patients with late-onset SpA were identified after a retrospective chart review of inpatients and outpatients seen during an eight-year period. These patients had significantly more cervical and lumbar pain, anterior chest involvement, number of inflamed peripheral joints, aseptic osteitis and systemic symptoms than patients with early-onset

SpA. A clear response to non-steroidal anti-inflammatory drugs (NSAIDs) was obtained more frequently in the late-onset patients than in the early-onset group. Two of the three patients with late-onset SpA not responding to NSAIDs were found to have Crohn's disease and were successfully treated with steroids. The results of this study are not comparable with the above (56, 57, 59) since 2 of the eight patients had IBD and 2 psoriasis at onset. In the late nineties, we collected a new series of consecutive HLA-B27-positive late onset uSpA patients (62) with the aim to verify the results of the previous study (59). Twenty patients (10 men and 10 women) were seen in the study period. Of these, 9 had 3 or more clinical and/or radiological manifestations of SpA, 5 showed 2, and 6 only 1. Six patients showed distal inflammatory swelling with pitting oedema on the dorsum of feet and/or hands. Three had a PMR-like syndrome at onset. Of the 20 patients, only 14 met the ESSG or the Amor criteria for SpA.

PsA frequently begins in the elderly. In a Finnish epidemiological study, 17 (26.1%) out of 65 incident cases of PsA started after the age of 55 (67). Punzi *et al.* have prospectively evaluated the presenting manifestations and the two-year outcome of 66 consecutive patients with PsA, 16 of whom with elderly onset and 50 with younger onset (68). The elderly group had a significant higher number of active joints, foot erosions and levels of serum CRP and synovial IL1 β and IL6 than younger patients. After two years, the progression rate of the joint damage and the CRP level were higher in elderly patients than in younger ones. A limitation of this study was that only patients with peripheral arthritis were considered. The frequent subset of patients with isolated peripheral enthesitis and/or dactylitis was ignored (69). In addition, none out of the 66 patients was reported having inflammatory swelling with pitting oedema on the dorsum of hands and/or feet. In a case-control study such inflammatory oedema was found in 39 (21%) out of 183 patients with PsA and in 18 (4.9%) out of 366 controls (70). The lower limbs were more frequently

involved than the upper ones asymmetrically. Lopez-Montilla and co-workers compared 12 patients with onset of PsA after the age of 60 with 84 with the onset in the previous decades. The elderly patients had a more frequent peripheral involvement (71). Peripheral arthritis was found by Kay and Walker in 5 patients with psoriatic SpA with onset of the disease at the age 55 or older (72). ReA has rarely been observed in the elderly. Four out of the 105 patients with seronegative arthritis reported by Dubost *et al.* had ReA (57).

IBD related arthritis has also been described in old age but its precise frequency has not been ascertained.

Differential diagnosis

Usually, the diagnosis of late-onset uSpA is not difficult. Most patients show two or more clinical manifestations of SpA, have family history of SpA and/or the B27 antigen and meet the Amor and the ESSG criteria for SpA. The possibility that some patients show for years only one manifestation should be kept in mind. Sometimes, the diagnosis can be rather difficult seeing that elderly patients often have several different musculoskeletal problems at the same time.

A special aspect of the differential diagnosis is the differentiation from other elderly-onset diseases showing inflammatory swelling with pitting oedema on the dorsum of hands and/or feet (73, 74). RS₃PE syndrome, first described in 1985 by McCarty and coworkers, is characterized by an acute onset of bilateral symmetrical synovitis involving predominantly the wrist, the carpus, the small hand joints and the flexor digitorum sheaths associated with a marked dorsal swelling of the hands with pitting oedema ("boxing-glove hand") (63, 64). Patients are persistently seronegative for the rheumatoid factor and show elevated acute phase reactants. The disease is very sensitive to small doses of steroids and remains in remission after the end of such therapy. Distal extremity swelling with pitting oedema over the dorsum of the hands and feet has also been described in patients with PMR (75-76) and giant cell arteritis (GCA) (77). The oedema may

be unilateral or bilateral with predominant involvement of the upper limbs. A 5-year prospective study has evaluated the relationship between "pure" RS₃PE syndrome and PMR with and without pitting oedema (78). No significant difference in the demographic, clinical and immunogenetic features were found between 23 patients with "pure" RS₃PE, 156 patients with PMR without pitting oedema and 21 patients with PMR with pitting oedema. Hand and foot magnetic resonance imaging showed that extensor synovitis was the responsible lesion for the oedema in the subcutaneous and peritendinous soft tissue of the dorsum in both conditions. These similarities suggest that PMR and RS₃PE syndrome are part of the clinical spectrum of the same disease. Independently of the extremity swelling with pitting oedema, PMR should be taken into account in the differential diagnosis since elderly-onset SpA may give a PMR-like syndrome (79, 80).

Other inflammatory diseases in which remitting distal extremity swelling with pitting oedema has been observed include: Whipple's disease, sarcoidosis, chondrocalcinosis, amyloid arthropathy, systemic lupus erythematosus, mixed connective disease, Sjögren's syndrome, systemic sclerosis, dermatomyositis and polyarteritis nodosa (81-89).

Lastly, distal extremity swelling with pitting oedema due to the involvement of tenosynovial extensor sheaths may be the first manifestation of haematologic and solid malignancies (90). Paraneoplastic remitting seronegative synovitis with pitting oedema may be unilateral or bilateral. Among the solid malignancies, adenocarcinoma of the prostate, stomach and colon are the most frequently reported. Non-Hodgkin lymphoma and chronic lymphoid leukemia are the most frequent associated haematologic malignancies.

In patients with elderly-onset SpA, care must be taken not to mistake spinal finding of diffuse idiopathic skeletal hyperostosis (DISH) for AS (58). DISH and SpA are completely different diseases having in common the involvement of axial skeleton and extraspinal entheses (91). DISH affects middle-

aged and elderly patients and is often asymptomatic or associated with mild dorsolumbar pain and/or slight restriction of spine movement. The radiological findings of spine involvement of SpA and DISH are so different that in patients with coexisting DISH and AS, it is possible to distinguish between the changes of the two diseases (58).

Treatment

Similarly to EORA, the management of late-onset SpA and late-onset PsA must take into account age-related changes in the pharmacokinetics and pharmacodynamics of drugs and the presence of conditions able to reduce medication adherence.

Patients with older onset AS should be treated following the recommendations proposed by the ASAS (Assessment in SpondyloArthritis International Society) and EULAR for AS of younger onset (92). Patients with late-onset uSpA should be treated according to the clinical presentation (peripheral arthritis, peripheral enthesitis, inflammatory swelling with pitting oedema, dactylitis, uveitis). NSAIDs, COX-2 inhibitors, local and systemic corticosteroids, sulphasalazine can be useful. Tumor necrosis factor α (TNF- α) blocking agent could be used in selected cases.

Patients with late-onset psoriatic arthritis should be treated according to the guidelines suggested by the GRAPPA (Group of Research and Assessment in Psoriasis and Psoriatic Arthritis) for the general management of patients with PsA (93). Attention should be paid to choose the best strategies to treat early PsA (94).

Conclusions

EORA is a heterogeneous disease, with a seropositive subset resembling classical RA and a more benign seronegative subset. Treatment should be tailored to disease severity taking into account comorbidities and other medications. Late-onset SpA shows the wide clinical spectrum of SpA of younger onset. The majority of cases enter in the uSpA and PsA subsets. Treatment should take in account the clinical presentations and follow recent international recommendations.

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