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

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 α2 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 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).

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

a) *Inflammatory diseases*
- Polymyalgia rheumatica
- Late-onset spondyloarthropathies (psoriatic arthritis, arthritis associated with inflammatory bowel disease, reactive arthritis, undifferentiated spondyloarthropathy)
- Crystal arthritis
- Paraneoplastic arthritis
- Viral arthritis

b) *Non-inflammatory diseases involving the shoulder girdle*
- Osteoarthritis
- Bilateral rotator cuff tendinitis
- Bilateral frozen shoulder
- Hypothyroidism
- Parkinson's disease

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 costitutional 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 RS_3PE (remitting, seronegative, symmetrical synovitis with pitting oedema) syndrome reported by McCarty and coworkers (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 inflammed 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 IL1β 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 elerly. 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). RS_3PE 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" RS_3PE 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 RS_3PE 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.

References

1. DEAL CL, MEENAN RF, GOLDENBERG DL *et al.*: The clinical features of elderly-onset rheumatoid arthritis. A comparison with younger-onset disease of similar duration. *Arthritis Rheum* 1985; 28: 987-94.
2. VAN SCHAARDENBURG D, BREEDVELD FC: Elderly-onset rheumatoid arthritis. *Semin Arthritis Rheum* 1994; 23: 367-78.
3. TERKELTAUB R, ESDAILE J, DECARY F, TANNENBAUM H: A clinical study of older age rheumatoid arthritis with comparison to a younger onset group. *J Rheumatol* 1983; 10: 418-24.
4. SALVARANI C, ZIZZI F, MACCHIONI PL *et al.*: [A clinical study on elderly-onset rheumatoid arthritis. Comparison with a group of patients with disease onset before age 60 years]. [Italian]. *Il Reumatologo* 1990; 3: 107-12.
5. EHRLICH GE, KATZ WA, COHEN SH: Rheumatoid arthritis in the aged. *Geriatrics* 1970; 25: 103-13.
6. PIPITONE N, PITZALIS C: [Arthritides in the elderly]. [Italian]. *Recenti Prog Med* 2004; 95: 432-42.
7. CECIL RL, KAMMERER WH: Rheumatoid arthritis in the aged. *Am J Med* 1951; 10: 439-45.
8. OLIVIERI I, PALAZZI C, PERUZ G, PADULA A: Management issues with elderly-onset rheumatoid arthritis: an update. *Drugs Aging* 2005; 22: 809-22.
9. BAJOCCHI G, LA CORTE R, LOCAPUTO A, GOVONI M, TROTTA F: Elderly onset rheumatoid arthritis: clinical aspects. *Clinical Exp Rheumatol* 2000; 18 (Suppl. 20): S49-50.
10. PUNZI L, BERTAZZOLO N, PIANON M, RIZZI E, ROSSINI P, TODESCO S: Synovial fluid levels of proinflammatory interleukins and their inter-relationships in elderly vs younger onset rheumatoid arthritis. *Aging* (Milano) 1996; 8: 277-81.
11. CHEN DY, HSIEH TY, CHEN YM, HSIEH CW, LAN JL, LIN FJ: Proinflammatory cytokine profiles of patients with elderly-onset rheumatoid arthritis: a comparison with younger-onset disease. *Gerontology* 2009; 55: 250-8.
12. CORRIGAN AB, ROBINSON RG, TERENTY TR, DICK-SMITH JB, WALTERS D: Benign rheumatoid arthritis of the aged. *Br Med J* 1974; 1: 444-6.
13. TURKCAPAR N, DEMIR O, ATLI T *et al.*: Late onset rheumatoid arthritis: clinical and laboratory comparisons with younger onset patients. *Arch Gerontol Geriatr* 2006; 42: 225-31.
14. BATHON JM, FLEISCHMANN RM, VAN DER HEIJDE D *et al.*: Safety and efficacy of etanercept treatment in elderly subjects with rheumatoid arthritis. *J Rheumatol* 2006; 33: 234-43.
15. GLENNAS A, KVIEN TK, ANDRUP O, KARSTENSEN B, MUNTHE E: Recent onset arthritis in the elderly: a 5 year longitudinal observational study. *J Rheumatol* 2000; 27: 101-8.
16. HANTZSCHEL H, BIRD HA, SEIDEL W *et al.*: Polymyalgia rheumatica and rheumatoid arthritis of the elderly: a clinical, laboratory, and scintigraphic comparison. *Ann Rheum Dis* 1991; 50: 619-22.

17. CECCATO F, ROVERANO S, BARRIONUEVO A, RILLO O, PAIRA S: The role of anticyclic citrullinated peptide antibodies in the differential diagnosis of elderly-onset rheumatoid arthritis and polymyalgia rheumatica. *Clin Rheumatol* 2006; 25: 854-7.
18. LOPEZ-HOYOS M, RUIZ DE ALEGRIA C, BLANCO R *et al.*: Clinical utility of anti-CCP antibodies in the differential diagnosis of elderly-onset rheumatoid arthritis and polymyalgia rheumatica. *Rheumatology* (Oxford) 2004; 43: 655-7.
19. PARODI M, GARLASCHI G, SILVESTRI E, CIMMINO MA: Magnetic resonance imaging in the differential diagnosis between polymyalgia rheumatica and elderly onset rheumatoid arthritis. *Clin Rheumatol* 2006; 25: 402-3.
20. SALVARANI C, CANTINI F, OLIVIERI I *et al.*: Proximal bursitis in active polymyalgia rheumatica. *Ann Intern Med* 1997; 127:27-31.
21. CANTINI F, SALVARANI C, NICCOLI L *et al.*: Fat suppression magnetic resonance imaging in shoulders of patients with polymyalgia rheumatica. *J Rheumatol* 2004; 31: 120-4.
22. CANTINI F, SALVARANI C, OLIVIERI I *et al.*: Shoulder ultrasonography in the diagnosis of polymyalgia rheumatica: a case-control study. *J Rheumatol* 2001; 28: 1049-55.
23. MORI S, KOGA Y, ITO K: Clinical characteristics of polymyalgia rheumatica in Japanese patients: evidence of synovitis and extracapsular inflammatory changes by fat suppression magnetic resonance imaging. *Mod Rheumatol* 2007; 17: 369-75.
24. SALVARANI C, CANTINI F, OLIVIERI I: Distal musculoskeletal manifestations in polymyalgia rheumatica. *Clin Exp Rheumatol* 2000; 18 (4 Suppl. 20): S51-2.
25. PEASE CT, HAUGEBERG G, MONTAGUE B *et al.*: Polymyalgia rheumatica can be distinguished from late onset rheumatoid arthritis at baseline: results of a 5-year prospective study. *Rheumatology* (Oxford) 2009; 48: 123-7.
26. PEASE CT, BHAKTA BB, DEVLIN J, EMERY P: Does the age of onset of rheumatoid arthritis influence phenotype?: a prospective study of outcome and prognostic factors. *Rheumatology* (Oxford) 1999; 38: 228-34.
27. CAPORALI R, MONTECUCCO C, EPIS O, BOBBIO-PALLAVICINI F, MAIO T, CIMMINO MA: Presenting features of polymyalgia rheumatica (PMR) and rheumatoid arthritis with PMR-like onset: a prospective study. *Ann Rheum Dis* 2001; 60: 1021-4.
28. HEALEY LA: Polymyalgia rheumatica and seronegative rheumatoid arthritis may be the same entity. *J Rheumatol* 1992; 19: 270-2.
29. SALVARANI C, MACCHIONI P, MANTOVANI W, PORTIOLI I: Polymyalgia rheumatica and seronegative rheumatoid arthritis: some considerations based on a northern Italian population. *J Rheumatol* 1993; 20: 756-7.
30. GONZALEZ-GAY MA, HAJEER AH, DABABNEH A *et al.*: Seronegative rheumatoid arthritis in elderly and polymyalgia rheumatica have similar patterns of HLA association. *J Rheumatol* 2001; 28: 122-5.
31. COACCIOLI S, PINOCA F, GIULIANI M, LANDUCCI P, SABATINI C, PUXEDDU A: Definition of adult-onset rheumatoid arthritis from elderly-onset rheumatoid arthritis by studying T-lymphocyte subpopulations, their soluble receptors and soluble receptor of interleukin-2. *Clin Ter* 2007; 158: 303-6.
32. CUTOLO M, MONTECUCCO CM, CAVAGNA L *et al.*: Serum cytokines and steroidal hormones in polymyalgia rheumatica and elderly-onset rheumatoid arthritis. *Ann Rheum Dis* 2006; 65: 1438-43.
33. BIRD HA, ESSELINCKX W, DIXON AS, MOWAT AG, WOOD PH: An evaluation of criteria for polymyalgia rheumatica. *Ann Rheum Dis* 1979; 38: 434-9.
34. TAGGART AJ, McDERMOTT B, DELARGY M *et al.*: The pharmacokinetics of sulphasalazine in young and elderly patients with rheumatoid arthritis. *Scand J Rheumatol* 1987; 64 (Suppl.): 29-36.
35. KEAN WF, BELLAMY N, BROOKS PM: Gold therapy in the elderly rheumatoid arthritis patient. *Arthritis Rheum* 1983; 26: 705-11.
36. BIASI D, CARLETTO A, CARAMASCHI P, BAMBARA LM: [Treatment of rheumatoid arthritis of senile onset with methotrexate] [Italian]. *Recenti Prog Med* 1995; 86: 472-5.
37. NURCHIS P, SALVARANI C, ZIZZI F *et al.*: Rheumatoid arthritis in the elderly: frequency of side effects of parenteral and oral chrysotherapy. *Eur J Inter Med* 1994; 5: 1-7.
38. TUTUNCU Z, REED G, KREMER J, KAVANAUGH A: Do patients with older-onset rheumatoid arthritis receive less aggressive treatment? *Ann Rheum Dis* 2006; 65: 1226-9.
39. MAVRAGANI CP, MOUTSOPOULOS HM: Rheumatoid arthritis in the elderly. *Exp Gerontol* 1999; 34: 463-71.
40. WASSENBERG S, RAU R, STEINFELD P, ZEIDLER H: Very low-dose prednisolone in early rheumatoid arthritis retards radiographic progression over two years: a multicenter, double-blind, placebo-controlled trial. *Arthritis Rheum* 2005; 52: 3371-80.
41. KIRWAN JR: The effect of glucocorticoids on joint destruction in rheumatoid arthritis. The Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study Group. *N Engl J Med* 1995; 333: 142-6.
42. KEAN WF, ANASTASSIADES TP, DWOSH IL, FORD PM, KELLY WG, DOK CM: Efficacy and toxicity of D-penicillamine for rheumatoid disease in the elderly. *J Am Geriatr Soc* 1982; 30: 94-100.
43. DROSOS A: Methotrexate intolerance in elderly patients with rheumatoid arthritis: what are the alternatives? *Drugs Aging* 2003; 20: 723-36.
44. KHAN MA, VAN DER LINDEN SM: A wider spectrum of spondyloarthropathies. *Semin Arthritis Rheum* 1990; 20: 107-13.
45. AMOR B, DOUGADOS M, MIJIYAWA M: [Critères de classification des spondylarthropathies] [French]. *Rev Rhum* 1990; 57: 85-9.
46. DOUGADOS M, VAN DER LINDEN S, JUHLIN R *et al.*: The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. *Arthritis Rheum* 1991; 34: 1218-27.
47. OLIVIERI I, VAN TUBERGEN A, SALVARANI C, VAN DER LINDEN S: Seronegative spondyloarthritides. *Best Pract Res Clin Rheumatol* 2002; 16: 723-39.
48. TOUSSIROT E, WENDLING D: Late-onset ankylosing spondylitis and related spondyloarthropathies. Clinical and radiological characteristics and pharmacological treatment options. *Drugs Aging* 2005; 22: 451-69.
49. BENNETT PH, BURCH TA: Population studies of rheumatic diseases. Amsterdam: *Excerpta Medica Foundation* 1968: 456-7.
50. VAN DER LINDEN S, VALKENBURG HA, CATS A: Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984; 27: 361-8.
51. VAN DER LINDEN SM, VALKENBURG HA, DE JONGH BM, CATS A: The risk of developing ankylosing spondylitis in HLA-B27 positive individuals. A comparison of relatives of spondylitis patients with the general population. *Arthritis Rheum* 1984; 27: 241-9.
52. DUBOST JJ, SAUVEZIE B: Actualités des rhumatismes inflammatoires du sujet âgé. *Rev Rhum Mal Osteoartic* 1992; 59 (6 bis): S37-42.
53. CARBONE LD, COOPER C, MICHET CJ, ATKINSON EJ, O'FALLON WM, MELTON LJ 3RD: Ankylosing spondylitis in Rochester, Minnesota, 1935-1989. Is the epidemiology changing? *Arthritis Rheum* 1992; 35: 1476-82.
54. FELDTKELLER E, BRUCKEL J, KHAN MA: Scientific contributions of ankylosing spondylitis patient advocacy groups. *Curr Opin Rheumatol* 2000; 12: 239-47.
55. FELDTKELLER E, KHAN MA, VAN DER HEIJDE D, VAN DER LINDEN S, BRAUN J: Age at disease onset and diagnosis delay in HLA-B27 negative vs. positive patients with ankylosing spondylitis. *Rheumatol Int* 2003; 23: 61-6.
56. DUBOST JJ, SAUVEZIE B: Late onset peripheral spondyloarthropathy. *J Rheumatol* 1989; 16: 1214-17.
57. DUBOST JJ, RISTORI JM, ZMANTAR C, SAUVEZIE B: [Rhumatismes séronégatifs a début tardif: Fréquence et atypies des spondylarthropathies] [French]. *Rev Rhum Mal Osteoartic* 1991; 58: 577-84.
58. OLIVIERI I, ORANGES GS, SCONOSCIUTO F, PADULA A, RUJU GP, PASERO G: Late onset peripheral seronegative spondyloarthropathy: report of two additional cases. *J Rheumatol* 1993; 20: 390-3.
59. OLIVIERI I, PADULA A, PIERRO A, FAVARO L, ORANGES GS, FERRI S: Late onset undifferentiated seronegative spondylarthropathy. *J Rheumatol* 1995, 22: 899-903.
60. CAPLANNE D, TUBACH F, LE PARC JM: Late onset spondylarthropathy: Clinical and biological comparison with early onset patients. *Ann Rheum Dis* 1997; 56: 176-9.
61. OLIVIERI I, SALVARANI C, CANTINI F, CIANCIO G, PADULA A: Ankylosing spondylitis and undifferentiated spondyloarthropathies: a clinical review and description of a disease subset with older age at onset. *Curr Opin Rheumatol* 2001; 13: 280-4.
62. OLIVIERI I, PADULA A, CIANCIO G, CANTINI F, SALVARANI C, GONZALEZ-GAY MA: Late onset HLA-B27-positive undifferentiated spondyloarthropathy: a new series of 20 patients. *Arthritis Rheum* 2001; 44 (Suppl.): S94.
63. McCARTY DJ, O'DUFFY JD, PEARSON L, HUNTER JB: Remitting seronegative symmetrical synovitis with pitting edema. RS3PE syndrome. *JAMA* 1985; 254: 2763-7.

64. RUSSELL EB, HUNTER JB, PEARSON L, MCCARTY DJ: Remitting seronegative, symmetrical synovitis with pitting edema – 13 additional cases. *J Rheumatol* 1990; 17:633-9.
65. OLIVIERI I, PADULA A, FAVARO L, PIERRO A, ORANGES GS, FERRI S: Dactylitis with pitting edema of the hand in longstanding ankylosing spondylitis. *Clin Rheumatol* 1995; 14: 701-4.
66. KOEGER AC, KARMOCHKINE M, CHAÏBI P: RS3PE syndrome associated with advanced ankylosing spondylitis. *J Rheumatol* 1995; 22: 375-6.
67. KAIPIAINEN-SEPPÄNEN O: Incidence of psoriatic arthritis in Finland. *Br J Rheumatol* 1996; 35: 1289-91.
68. PUNZI L, PIANON M, ROSSINI P, SCHIAVON F, GAMBARI PF: Clinical and laboratory manifestations of elderly onset psoriatic arthritis: A comparison with younger onset disease. *Ann Rheum Dis* 1999; 58: 226-9.
69. SALVARANI C, CANTINI F, OLIVIERI I *et al*.: Isolated peripheral enthesitis and/or dactylitis: A subset of psoriatic arthritis. *J Rheumatol* 1997; 24: 1106-10.
70. CANTINI, SALVARANI C, OLIVIERI I *et al*.: Distal extremity swelling with pitting edema in psoriatic arthritis: A case-control study. *Clin Exp Rheumatol* 2001; 19: 291-6.
71. LÓPEZ-MONTILLA MD, GONZÁLEZ J, MARTÍNEZ FG, FERNÁNDEZ-MORENO JR, COLLANTES E: Clinical features of late onset psoriatic arthritis. *Exp Gerontol* 2002; 37: 441-3.
72. KAY LJ, WALKER DJ: Late onset spondyloarthropathy: comparison with early onset patients. *Ann Rheum Dis* 1997; 56: 572.
73. OLIVIERI I, SALVARANI C, CANTINI F: Remitting distal extremity swelling with pitting edema: A distinct syndrome or a clinical feature of different inflammatory rheumatic diseases? *J Rheumatol* 1997; 24: 249-52.
74. OLIVIERI I, SALVARANI C, CANTINI F: RS3PE syndrome: an overview. *Clin Exp Rheumatol* 2000; 18 (Suppl. 20): 53-5.
75. SALVARANI C, GABRIEL S, HUNDER GG: Distal extremity swelling with pitting edema in polymyalgia rheumatica. Report on nineteen cases. *Arthritis Rheum* 1996; 39: 73-80.
76. SALVARANI C, CANTINI F, MACCHIONI P *et al*.: Distal musculoskeletal manifestations in polymyalgia rheumatica: A prospective followup study. *Arthritis Rheum* 1998; 41: 1221-6.
77. SALVARANI C, HUNDER GG: Musculoskeletal manifestations in a population-based cohort of patients with giant cell arteritis. *Arthritis Rheum* 1999; 42: 1259-66.
78. CANTINI F, SALVARANI C, OLIVIERI I *et al*.: Remitting sieronegative symmetrical synovitis with pitting oedema (RS3PE) syndrome: A prospective follow up and magnetic resonance imaging study. *Ann Rheum Dis* 1999; 58: 230-6.
79. GONZÁLEZ-GAY MA, GARCÍA-PORRÚA C, SALVARANI C, OLIVIERI I, HUNDER GG: Polymyalgia manifestations in different conditions mimicking polymyalgia rheumatica. *Clin Exp Rheumatol* 2000; 18: 755-9.
80. OLIVIERI I, GARCIA-PORRUA C, PADULA A, CANTINI F, SALVARANI C, GONZALEZ-GAY MA: Late onset undifferentiated spondyloarthritis presenting with polymyalgia rheumatica features: description of seven cases. *Rheumatol Int* 2007; 27: 927-33.
81. OLIVIERI I, BRANDI G, PADULA A *et al*.: Lack of association with spondyloarthitis and the HLA-B27 in Italian patients with Whipple's disease. *J Rheumatol* 2001; 28: 1294-7.
82. CANTINI F, NICCOLI L, OLIVIERI I *et al*.: Remitting distal lower extremity swelling with pitting oedema in acute sarcoidosis. *Ann Rheum Dis* 1997; 56: 565-6.
83. IKE RW, BLAIVAS M: Corticosteroid responsive puffy hands and occult vasculitis neuropathy: RS3PE plus? *J Rheumatol* 1993: 20: 205-6.
84. SCHAEVERBEKE T, FATOUT E, MARCÉ S *et al*.: Remitting seronegative symmetrical synovitis with pitting oedema: disease or syndrome? *Ann Rheum Dis* 1995; 54: 681-4.
85. BILLEY T, NAVAUX F, LASSOUED S: Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) as the first manifestation of periarteritis nodosa. Report of a case. *Rev Rheum* [Engl ed] 1995; 62: 53-4.
86. GUMÁ M, CASADO E, TENA X, OLIVÉ A: RS3PE: Six years later. *Ann Rheum Dis* 1999; 58: 722-3.
87. MCCARTY DJ: *Clinical picture of rheumatoid arthritis*. *Arthritis and Allied Conditions*, 12th edition. Edited by MCCARTY DJ, KOOPMAN WJ. MALVERN, PA: Lea and Febiger; 1993: n781-809.
88. MAGY N, MICHEL F, AUGE B, TOUSSIROT E, WENDLING D: Amyloid arthropathy revealed by RS3PE syndrome. *Joint Bone Spine* 2000; 67: 475-7.
89. PITTAU E, PASSIU G, MATHIEU A: Remitting asymmetrial pitting oedema in systemic lupus erythematosus: two cases studied with magnetic resonance imaging. *Joint Bone Spine* 2000; 67: 544-9.
90. CANTINI F, SALVARANI C, OLIVIERI I: Paraneoplastic remitting seronegative symmetrical synovitis with pitting edema. *Clin Exp Rheumatol* 1999; 17: 741-4.
91. OLIVIERI I, D'ANGELO S, PALAZZI C, PADULA A, MADER R, KHAN MA: Diffuse idiopathic skeletal hyperorostosis: a condition that needs to be differentiated from spondyloarthritis. *Curr Rheumatol Rep* (in press).
92. ZOCHLING J, VAN DER HEIJDE D, BURGOS-VARGAS R *et al*.: ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann Rheum Dis* 2006; 65: 442-52
93. RICHLIN CT, KAVANAUGH A, GLADMAN DD *et al*.: Treatment recommendations for psoriatic arthritis. *Ann Rheum Dis* 2009; 68: 1387-94.
94. OLIVIERI I, D'ANGELO S, PALAZZI C, PADULA A: Treatment strategies for early psoriatic arthritis. *Expert Opin Pharmacother* 2009; 10: 271-82.