Arthritis in Idiopathic Inflammatory Myopathy: Clinical Features and Autoantibody Associations

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ABSTRACT. ***Objective.*** To determine the prevalence, distribution, and clinical manifestations of arthritis in a cohort of patients with idiopathic inflammatory myopathies (IIM). Associations with autoantibody status and HLA genetic background were also explored.

Methods. Consecutive patients with IIM treated in a single center were included in this cross-sectional study (n = 106). History of arthritis, 68-joint and 66-joint tender and swollen joint index, clinical features of IIM, and autoantibody profiles were obtained by clinical examination, personal interview, and review of patient records. High-resolution genotyping in HLA-DRB1 and HLA-DQB1 loci was performed in 71 and 73 patients, respectively.

Results. A combination of patients' medical history and cross-sectional physical examination revealed that arthritis at any time during the disease course had occurred in 56 patients (53%). It was present at the beginning of the disease in 39 patients (37%) including 23 cases (22%) with arthritis preceding the onset of muscle weakness. On physical examination, 29% of patients had at least 1 swollen joint. The most frequently affected areas were wrists, and metacarpophalangeal and proximal interphalangeal joints. Twenty-seven out of the 29 anti-Jo1-positive patients had arthritis at any time during the course of their illness; this prevalence was significantly higher compared to patients without the anti-Jo1 autoantibody ($p < 0.0001$). No association of arthritis with individual HLA alleles was found.

Conclusion. Our data suggest that arthritis is a common feature of myositis. It is frequently present at the onset of disease and it may even precede muscular manifestations of IIM. The most common presentation is a symmetrical, nonerosive polyarthritis affecting particularly the wrists, shoulders, and small joints of the hands. We have confirmed a strong association of arthritis with the presence of the anti-Jo1 antibody. (J Rheumatol First Release May 1 2014; doi:10.3899/jrheum.131223)

Key Indexing Terms:
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Idiopathic inflammatory myopathies (IIM) represent a group of systemic autoimmune disorders characterized by a nonsuppurative inflammation of skeletal muscles as the major manifestation. Distinct subgroups of IIM with variable clinical and laboratory manifestations are recognized, such as polymyositis (PM), dermatomyositis (DM), juvenile dermatomyositis, cancer-associated myositis, immune-mediated necrotizing myopathy, and inclusion body myositis (IBM).

Arthritis is commonly seen in patients with IIM; however, comprehensive data on its presentation and on manifestations in individual myositis subgroups are scarce[1]. Arthritis is particularly frequent in patients with autoantibodies directed against tRNA synthetases as part of the antisynthetase syndrome[2,3,4,5,6], but it is not limited to this subgroup[7,8]. Arthritis and/or arthralgias were reported in 33% of patients with IIM in a large multicenter Japanese cohort used for a formulation of new classification criteria, in which arthritis was included[9]. Other available information originates from case reports[10,11,12,13] or small cohorts selectively defined by the presence of a specific autoantibody or antisynthetase syndrome[5,14,15,16]. Arthritis in patients with IIM is considered less severe and less destructive when compared to the joint involvement in rheumatoid arthritis (RA), but the few available reports provide conflicting results on this aspect[5,9,10,11,12,13,14,15,16]. The degree of reported joint involvement in myositis varies from nonerosive arthritis[12] and subluxing arthropathy[5] to erosive and destructive arthritis[10,13,14].

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The aim of our study was to provide comprehensive data regarding joint involvement in unselected patients with IIM from a single center. Specifically, we determined the prevalence of arthritis in patients with IIM, its relation to the course of the muscle disease, characteristics of arthritis such as distribution and extent, as well as its association with autoantibody profiles and HLA allelic polymorphisms.

MATERIALS AND METHODS

Patients and controls. All patients with IIM fulfilling diagnostic criteria seen both at the outpatient and inpatient departments of the Institute of Rheumatology between January and September 2012 were recruited into the study. The diagnosis of PM and DM was based on the criteria of Bohan and Peter[17,18], necrotizing myopathy and amyopathic DM were diagnosed using the European Neuromuscular Centre Workshop (ENMC) criteria[19], and the diagnosis of IBM was established using the Griggs criteria[20]. All patients had a muscle biopsy performed during the course of their disease; however, the full description of the findings required for classification according to the ENMC criteria was available only for the 76 biopsies performed after 2004. The control group for the genetic substudy consisted of 179 healthy subjects. The study was approved by the ethics committee at the Institute of Rheumatology and all patients gave informed consent.

Clinical data. Basic demographic and clinical data including the history of IIM onset, disease course, smoking history, and presence of lung involvement (defined as a presence of active alveolitis or fibrotic changes on radiograph or high-resolution computed tomography scan, and/or DLCO < 70%) were obtained from all patients. Information regarding presence or absence of arthritis in the past and/or at the current time with respect to the onset, localization, and symmetry as well as other features of joint involvement such as presence of joint deformities ("floppy thumb") was obtained during personal interviews with patients and/or from medical records. Activity of arthritis and the degree of joint involvement were assessed by both patients and physicians using visual analog scales (VAS). A semiquantitative scale was used to evaluate the severity of joint involvement as a proportion of total morbidity. History of arthritis was established if the patient during personal interview reported having at least 1 painful and swollen joint in the past or if the presence of inflammatory arthritis detected by an experienced rheumatologist was recorded in the medical records. Current arthritis was defined as a presence of at least 1 swollen joint on physical examination using the 68/66-joint count. Radiographs of the joints of hands and/or feet were available from 47 patients.

Autoantibodies. Autoantibody profiles of patients with IIM were determined during routine diagnostic examination using indirect immunofluorescence to screen for antinuclear antibodies (ANA) and anti-dsDNA (Immuno Concepts), line immunoassay (Imtec Human), and Western blot-myositis (Euroimmun) for detection of individual autoantibodies directed against Jo-1, Mi-2, Ku, PM-Scl, PM-Scl75, PM-Scl100, PL-7, PL-12, EJ, OJ, SRP, Ro, Ro52, La, Scl-70, and U1-RNP antigens. In-house- made 35S radioimmunoprecipitation[21] was used to confirm the results and to detect autoantibodies not identified using commercial assays [against: transcriptional intermediary factor 1-γ (TIF1-γ), MDA5, NXP2, Zo, EIF, RNAP I (RNA polymerase antibodies), RNAP II, and RNAP III]. Rheumatoid factors (RF) were detected using a particle-agglutination assay (Fujirebio Inc.), and an ELISA test for anticyclic citrullinated peptide (anti-CCP; TestLine Clinical Diagnostics) was used to detect anticitrullinated protein antibodies (ACPA).

HLA typing. Allelic polymorphism of HLA-DRB1 and HLA-DQB1 genes was analyzed by DNA-based typing using commercial sets (OneLambda) according to manufacturer's instructions.

Statistics. Demographics, clinical characteristics, and results are presented as descriptive statistics. The continuous not-normally distributed variables were analyzed by Mann-Whitney test; categorical data were analyzed by Fisher's exact test having p values estimated by Monte Carlo simulations (n = 10,000), and Kaplan-Meier estimator was used for calculation of survival analysis of arthritis. The significance of differences in allele and gene frequencies was evaluated by Fisher's exact test. We used GraphPad Prism 5 (GraphPad Software), QuickCalcs online calculator (graphpad.com), and R (r-project.org) for statistical analyses. P values < 0.05 were considered statistically significant.

RESULTS

Demographic and clinical data of patients. In total, 106 patients with IIM were included in the study. Basic demographic and clinical characteristics are summarized in Table 1.

Prevalence and characteristics of joint involvement. Combining patients' medical history and cross-sectional physical examination revealed that arthritis at any time during the disease course had occurred in 56 patients (52.8%; Table 2). Thirty-nine patients (36.8%) had arthritis at disease onset.

Thirty-one patients (29.2%) presented with at least 1 swollen joint at the time of cross-sectional evaluation. Nine additional patients had only joint tenderness, with no swelling. We did not find any difference in the prevalence of arthritis among individual IIM subgroups.

Table 1. Demographic and basic clinical data.

Patients, n	106
Sex; male/female	32/74
Age, yrs	
Mean ± SD	55.6 ± 14.1
Median (95% CI)	59 (52.8–58.3)
Diagnosis[a]	PM = 46[†] (43.4%)
	Definite/probable/possible 26/11/9
	DM = 40[§‡] (37.7%)
	Definite/probable/possible 35/3/2
	CAM = 8 (7.5%)
	IMNM = 11 (7.5%)
	IBM = 1 (0.9%)
Disease duration, yrs[b]	
Whole group	6.1 ± 6.3 (4.4, 4.9–7.3)
Arthritis patients	6.8 ± 5.7 (5.0, 5.3–8.3)[*]
Nonarthritis patients	5.3 ± 6.8 (3.0, 3.3–7.2)[*]
Lung involvement	37 (34.9%)
Ever smokers	40 (37.7%)

[a] Muscle biopsy evaluable according to the ENMC criteria was available in 76 patients: 25 patients satisfied biopsy criteria for PM, 28 for DM, 11 for IMNM, 1 for IBM; 9 biopsies did not have typical changes, and 2 were nonclassifiable, with significant pathologies, but not consistent with a single diagnostic category[19]. [†] Including 5 patients with overlap syndromes: 3 systemic sclerosis (SSc), 1 Sjögren syndrome (SS), and 1 rheumatoid arthritis. [§] Including 1 patient with clinically amyopathic dermatomyositis. [‡] Including 3 patients with overlap syndromes: 2 SSc and 1 SS. [b] Shown as mean ± SD (median, 95% CI). [*] A significant difference was found between disease duration in arthritis and nonarthritis patients (p = 0.04). ENMC: European Neuromuscular Centre Workshop; PM: polymyositis; DM: dermatomyositis; CAM: cancer-associated myositis; IMNM: immune-mediated necrotizing myopathy; IBM: inclusion body myositis.

Table 2. Arthritis in myositis subtypes. Data are n (%).

Diagnosis	Arthritis at Any Time*	Arthritis at Disease Onset**	Current Arthritis# (≥ 1 swollen joint)
PM (46)	27 (59)	19 (41)	17 (40)
DM (40)	22 (55)	15 (38)	11 (28)
CAM (8)	2 (25)	1 (13)	0 (0)
IMNM (11)	4 (36)	1 (13)	2 (18)
IBM (1)	1 (100)	1 (100)	1 (100)
Total (106)	56 (53)	39 (37)	31 (29)

*Combination of patient history and clinical examination; ** Based on patient history; # Arthritis present at the time of evaluation. PM: polymyositis; DM: dermatomyositis; CAM: cancer associated myositis; IMNM: immune mediated necrotizing myopathy; IBM: inclusion body myositis.

Probability of arthritis development. Patients with arthritis had significantly longer disease duration than those without arthritis (p = 0.04; Table 1). Patients who did not have arthritis at disease onset have a 65.6% (95% CI 57.1–75.2) overall probability of its future development and this probability gradually decreases to 33.9% (95% CI 23.6–48.7) after 10 arthritis-free years (Figure 1). Thus, the probability of having arthritis increases with the disease duration up to 66.1% (95% CI 51.3–76.4) after 10 years.

Arthritis at disease onset. Out of the 39 patients who had arthritis at the onset of IIM, joint symptoms preceded muscle weakness in 23 patients (59%) and occurred simultaneously in 16 (41%). Arthritis most commonly manifested as symmetrical polyarthritis in 33 cases (84.6%); oligoarthritis (involvement of 2–4 joints) and monoarthritis occurred in 5 (12.8%) and in 1 (2.6%) patient, respectively.

Current arthritis at the time of evaluation. Out of the 31 patients (29.2%) presenting with at least 1 swollen joint at the cross-sectional evaluation, 5, 14, and 12 patients had 1, 2–4, and more than 4 swollen joints, respectively. One patient had a newly diagnosed swollen joint at this examination for the first time.

Mean affected/tender/swollen joint counts in patients with arthritis were 8.3 ± 9.1, 8.4 ± 9.4, and 5.3 ± 5.4, respectively. Metacarpophalangeal (MCP) and proximal interphalangeal joints of the fingers and thumbs, wrists, and shoulders were the most frequently involved joints (Table 3).

Other forms of joint involvement. Deforming arthropathy was present in 15 patients (14.2%). Extreme lateral instability of the first interphalangeal joint ("floppy thumb") occurred in 5 patients (4.7%); 4 of them had anti-Jo1-positive PM, and 1 had anti-Mi-2-positive DM. Deformity in the first MCP was present in 3 patients (2.8%). All other deformities affected separate individual joints. Five patients (4.7%) had more than 1 joint deformity.

Radiographic characteristics of joint involvement. Radiographs of peripheral joints were available in 47 patients. Forty-six and 37 patients had radiographs of the hands and feet, respectively. Out of the 15 patients with clinically apparent deforming arthropathy, radiographs were available in 9 (60%). Joint erosions were present in 2 patients:

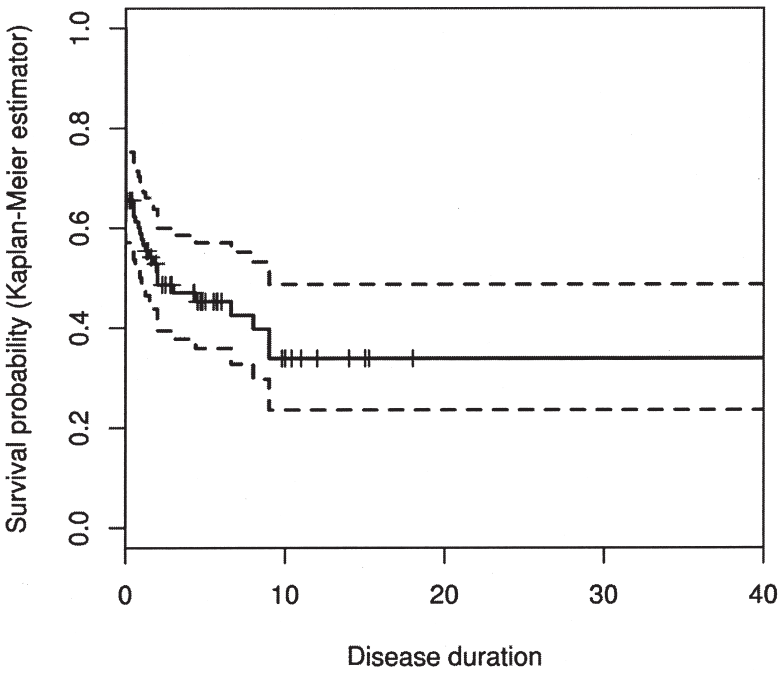

Figure 1. Probability of survival without arthritis. Probability of future development of arthritis in patients with arthritis-free survival (solid line) with 95% CI (dashed lines). Crosses (+) indicate censoring.

Table 3. Distribution of arthritis at the time of examination.

Joint	No. Patients with Affected Joints (%)		
	Tender	Swollen	Tender and/or Swollen
Temporomandibular	7 (6.6)	1 (0.9)	7 (6.6)
Sternoclavicular	7 (6.6)	2 (1.9)	7 (6.6)
Acromioclavicular	13 (12.3)	0	13 (12.3)
Shoulder	22 (20.8)	0	22 (20.8)
Elbow	14 (13.2)	5 (4.7)	14 (13.2)
Wrist	20 (18.9)	11 (10.4)	23 (21.7)
Metacarpophalangeal I-V	18 (16.9)	12 (11.3)	22 (20.8)
Proximal interphalangeal I-V	20 (18.9)	20 (18.9)	22 (20.8)
Distal interphalangeal II-V	6 (5.7)	5 (4.7)	7 (6.6)
Hip	4 (3.8)	—	4 (3.8)
Knee	9 (8.5)	3 (2.8)	10 (9.4)
Ankle	12 (11.3)	6 (5.7)	13 (12.3)
Tarsal joint	11 (10.4)	3 (2.8)	13 (12.3)
Metatarsophalangeal I-V	11 (10.4)	1 (0.9)	11 (10.4)
Interphalangeal I-V	2 (1.9)	0	2 (1.9)
Patients with at least 1 joint affected	45 (42.5)	31 (29.2)	52 (49)

destructive arthritis of carpal joints in a patient with an overlap of PM with RA with a positivity of RF and anti-CCP autoantibodies; and destructive arthritis of the second and third metatarsophalangeal joints in 1 patient who was anti-Jo1-positive for DM.

Clinical aspects of IIM with arthritis. Myositis relapsed in 31 patients (29.2%) at any time during the course of the illness. Arthritis was a feature of the relapse in 15 patients (48.4%) and occurred most frequently concurrently with the myositis flare (8 cases; 53.3%) or shortly before or after the relapse of other myositis symptoms in 4 and 2 patients, respectively; temporal pattern was not specified in 1 patient. The most common manifestation of arthritis during IIM relapses was polyarthritis or oligoarthritis in 7 and 6 patients, respectively (46.7 and 40%); detailed data on the number of affected joints were not available in 2 individuals.

Arthritis was present at disease onset in 13 out of 31 patients (41.9%) who later relapsed and in 29 out of 75 (38.7%) who did not. Thus, the presence of arthritis at the early phase of the disease is not predictive of future myositis relapses ($p = 0.8$). Similarly, the presence of arthritis at disease onset does not predict whether the relapse will be associated with arthritis ($p = 0.16$).

Clinical relevance of arthritis. Arthritis activity and joint damage was assessed using a VAS by both the patient and the evaluating physician. The mean arthritis activity and joint damage scores were relatively low in the whole group owing to a significant proportion of unaffected individuals. However, in patients with joint involvement, both mean activity of arthritis and joint damage were considered to be moderate (Table 4). Joint disease activity was rated higher by patients than by physicians ($p = 0.01$). When joint disease was considered as a proportion of total morbidity on a semiquantitative scale, 66 patients (62.3%) felt that arthritis did not play any role in the disease burden. Contribution of arthritis to the overall morbidity was reported to be small by 24 patients (22.6%), medium by 9 (8.5%), and large by 7 (6.6%).

Table 4. Arthritis activity and damage. Data shown as mean ± SD (n).

	All Patients	Patients with VAS > 0
MD activity	7.5 ± 15.8	19.4 ± 20.5 (41)
MD damage	6.2 ± 15.6	21.2 ± 22.8 (31)
Pt activity	14.0 ± 21.5	26.5 ± 23.4 (56)

MD/Pt: Physician's/patient's assessment of activity/damage on visual analog scale (VAS; 100 mm).

Autoantibodies. Myositis-specific and myositis-associated autoantibodies were tested in all patients and most patients were also evaluated for the presence of additional autoantibodies associated with other rheumatic diseases with frequent joint involvement (i.e., RA, systemic lupus erythematosus, Sjögren syndrome, and systemic sclerosis). Autoantibodies were found in 87 patients (82.1%). Not surprisingly, a strong association of anti-Jo1 antibodies with arthritis was confirmed, with 27 out of 29 anti-Jo1-positive patients (93%) having arthritis at some point during the course of IIM. The incidence of arthritis among anti-Jo1-positive patients was significantly higher compared to the anti-Jo1-negative subjects ($p < 0.0001$). No significant association between arthritis and autoantibody positivity could be found for ANA (positive in 42.6% of tested patients), RF (10.2%), anti-Ro52 (32.7%), anti-Ro (11.5%), anti-PM-Scl (12.3%), anti-Mi-2 (6.7%), and anti-TIF-1γ (8.2%). Other autoantibodies were found in very low frequencies and could not be statistically evaluated. Seven

of 9 RF-positive patients and both patients with ACPA had arthritis. ACPA were positive at relatively high levels (patient No. 2: 239 U/l, patient No. 99: 114 U/l). Only patient No. 2 fulfilled the 1987 American College of Rheumatology (ACR) classification criteria for RA and was classified with an overlap syndrome.

Arthritis and HLA status. Allelic polymorphism of HLA-DRB1 and -DQB1 genes was analyzed in 71 and 73 patients and 179 and 175 healthy controls, respectively. Patients had higher frequencies of HLA-DRB1*03 (56%) and HLA-DQB1*02 (70%) alleles in comparison with the control group (25% and 42%; $p < 0.0001$), but no evidence of an association between arthritis and these or any other HLA-DRB1 or -DQB1 alleles was observed (from $p = 0.2205$ to $p = 1.0000$).

DISCUSSION

We present patient history as well as cross-sectional data regarding joint involvement in a cohort of 106 consecutive patients with IIM seen between January and September 2012 in a single center. To our knowledge, our study represents the largest comprehensive overview of arthritis in an unselected cohort of such patients. The results show that arthritis is a common feature of myositis, affecting more than half of patients overall. Individual subtype of IIM most likely does not play a role in prevalence of arthritis. In the majority of patients with arthritis it manifests already at the onset of IIM, preceding symptoms of muscle weakness in half and appearing simultaneously in another one-third. Survival analysis shows that the highest probability of future development of arthritis is at the beginning of the muscle disease, gradually decreasing for up to 10 years of disease duration, with a significant residual risk even after that time (Figure 1). This is supported by the fact that patients with arthritis had longer mean disease durations. We may hypothesize that joint tenderness, without swelling, found in 9 patients at cross-sectional examination might represent the first sign of newly developing arthritis in these patients.

Arthritis is also a common feature of disease relapses, being present in about half of relapsing patients, most frequently occurring at the same time as the muscle symptoms. However, arthritis at the myositis onset is not predictive of the presence of arthritis during myositis relapses or of any future relapses of IIM.

The most frequently involved joints are the shoulders and small joints of the hands — wrists, metacarpophalangeal and proximal interphalangeal joints (each affecting about one-fifth of the patients), followed by elbows, ankles, and tarsal and acromioclavicular joints. The involvement of hand joints mimicking the distribution of involvement in RA together with the fact that arthritis often precedes the onset of muscle weakness may contribute to an occasional misdiagnosis of IIM as RA[22].

We have combined data obtained both in retrospective and cross-sectional fashion; therefore we were not able to use a uniform definition of inflammatory arthritis. For the purpose of retrospective analysis, arthritis was defined as either an inflammatory arthritis diagnosed by a rheumatologist in the past and documented in the medical records or as a presence of both joint swelling and pain reported by the patient during the interview. Every attempt was made to confirm the inflammatory nature of the joint involvement and to rule out symptoms that could have been caused by osteoarthritis. For this reason a more stringent definition of arthritis requiring a simultaneous presence of both joint swelling and pain was applied. We are aware that, despite our efforts, retrospectively collected data might have caused arthritis overestimation. However, relying on medical records only would miss many arthritis cases, because especially mild and transitory forms of arthritis could have gone unreported.

Almost 30% of patients with IIM in our cohort had clinically apparent arthritis, defined as a presence of at least 1 swollen joint, at the time of cross-sectional evaluation. Polyarthritis was the most frequent manifestation with a mean of 5 affected joints. This suggests that, when specifically looked for, arthritis is a frequent manifestation of IIM.

In our cohort, a strong association of arthritis with the presence of the anti-Jo1 autoantibody was confirmed. The prevalence of arthritis among anti-Jo1-positive patients was over 93%, which is more than was reported in some other studies[14,23]. The distribution of affected joints in our anti-Jo1-positive patients was similar to previous reports and confirms a close relationship of joint disease with anti-Jo1 antibodies. We could not demonstrate an association of arthritis with the presence of any other autoantibody, presumably because of the low numbers of patients in other autoantibody subgroups. Indeed, an association of arthritis with 2 other antisynthetase antibodies, anti-PL-7[16] and anti-PL-12[24], has been recently described. In those studies, unlike in our cohort, patients were included on the basis of autoantibody positivity rather than the diagnosis of IIM, therefore introducing a selection bias. Seven of 9 RF-positive patients and both patients with ACPA had arthritis. Only 1 of those patients fulfilled the 1987 ACR classification criteria for RA. These findings are in contrast with reports[25,26] describing a relatively frequent overlap of IIM with RA, but are consistent with the original study of Bohan, *et al*, who observed this combination more rarely in 2.3% of patients[27], and also with other reports[28]. It may be clinically difficult to distinguish between arthritis as a manifestation of myositis and as a main clinical feature in RA, but the rare presence of typical deformities and radiographic erosions in those with available radiographs argues against the frequent existence of the overlap syndrome.

Association of HLA-DRB1 or HLA-DQB1 polymorphism with arthritis was not found. As expected, we

observed a higher frequency of HLA-DRB1*03 in our cohort. This allele has been associated with anti-Jo1 antibodies[29], but it may be present also in patients with some other autoantibodies or without them. The absence of the association of HLA-DRB1*03 and arthritis in our patients suggests that the presence of anti-Jo1 rather than HLA-DRB1*03 is the contributing factor.

Arthritis and joint involvement do not seem to significantly contribute to the overall disease burden in most patients with IIM. The activity of arthritis was generally considered to be low to moderate by both patients and physicians. Most patients assessed the contribution of arthritis to the overall morbidity to be none or only mild. It gives an impression that many patients perceive arthritis as less bothersome than other manifestations of myositis. However, in some patients arthritis contributes significantly to the overall morbidity. Seven patients judged the contribution of arthritis to be of large significance and in 2 of them the total morbidity was driven mostly by joint involvement. Moreover, nearly half of the IIM relapses were associated with arthritis. Therefore, in some patients arthritis may be the main complaint and the choice of drug therapy should reflect this. However, because it is not known what treatment is best for arthritis in myositis, the same drugs used to treat other IIM manifestations are usually prescribed.

Arthritis in IIM is rarely deforming or erosive. In our cohort, deforming arthropathy was present in 15% of patients and radiographic erosions were detected in only 2 patients (1 overlap syndrome with RA and 1 with anti-Jo1-positive DM); both patients had clinically apparent deformities. These findings may be limited because not all of our patients had radiographs performed. However, because the radiographs were indicated based on the presence and severity of joint involvement, it is likely that most, if not all, patients with radiographic changes were identified. Five of our patients had so-called floppy thumb deformity[30]; 4 of them (80%) were positive for anti-Jo1 autoantibody, thus confirming a previous report on this type of subluxing arthropathy[14].

We have documented that arthritis is a common, although usually not severe, feature of IIM. It is often present at the beginning of the disease, even preceding the onset of muscle weakness in a substantial proportion of patients. Distribution of the most frequently involved joints is similar to that seen in RA. In our group, arthritis was mostly not deforming, although we found some previously described characteristic deformities in some patients.

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