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INFLAMMATORY MUSCLE DISEASE (I LUNDBERG AND L DIEDERICHSEN, SECTION EDITORS)

Arthritis in Idiopathic Inflammatory Myopathies

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Abstract

Purpose of Review Arthritis is a well-recognized symptom of idiopathic inflammatory myopathies (IIM). We provide a summary of available data regarding the epidemiology, clinical characteristics, and autoantibody associations of joint involvement in various forms of IIM.

Recent Findings Arthritis is reported in 18–55% of patients with IIM. It is particularly frequent (20–70%) in those with antisynthetase syndrome (ASS); highest prevalence is associated with anti-Jo-1 positivity. Most common manifestation is non-erosive polyarthritis. X-ray erosions may be found occasionally in ASS, particularly in patients with overlap with rheumatoid arthritis (RA). Arthritis is often present at the time of IIM diagnosis and it may even precede the onset of muscle weakness. Arthritis may in some cases be the main disease manifestation responsible for the disease burden in patients with IIM.

Summary Arthritis is a frequent symptom of IIM. Polyarthritis of small joints of the hands is the most frequent clinical manifestation. Arthritis may be the first or dominant symptom in IIM and therefore patients may be initially misdiagnosed as having RA. Particularly in seronegative RA patients with interstitial lung disease or Raynaud's phenomenon, the possibility of IIM should be considered.

Keywords Idiopathic inflammatory myopathies · Arthritis · Antisynthetase syndrome · Floppy-thumb · Anti-Jo-1

Introduction

Idiopathic inflammatory myopathies (IIM) are a clinically heterogeneous group of diseases, which share muscle weakness caused by chronic inflammation of skeletal muscles as their major manifestation [1•, 2]. Arthritis, or joint involvement in general, has been widely recognized either as a manifestation of the disease itself or as a related symptom [2, 3]. There is a lack of systematic literature data regarding joint involvement in IIM and most information comes from case reports or small cohort studies [4, 5]. Several recent reports concentrate on joint involvement as a part of antisynthetase syndrome (ASS); however, arthritis can be present in most of the other subtypes of IMM as well. Since 1970, several sets of novel classification criteria for IIMs have been proposed [1•]. Only three of them include arthritis as a feature of IIM [6–8], despite the frequent occurrence of joint symptoms in IIM patients. This is likely related to the fact that arthritis in IIM often mimics other arthritides such as rheumatoid arthritis (RA) and therefore lacks specificity needed for classification purposes.

Prevalence of Arthritis in IIM

Reported prevalence of arthritis in IIM patients varies between 18 and 53% according to studies that included at least 20 subjects [4–20] (Table 1). The wide range of reported prevalence can be explained by differences between individual cohorts and by the fact that various definitions of arthritis and joint involvement in general were used. Love et al. identified in a cohort of 181 IIM patients 85 (47%) individuals with arthritis [6]. Although patients with overlap syndromes who besides myositis also

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Table 1 Clinical studies describing joint involvement in idiopathic inflammatory myopathies and antisynthetase syndrome

Authors, year (reference)	Diagnosis	*n*	Type of joint involvement	Arthritis at diagnosis %	Arthritis at follow-up % (median, years)
Bernstein et al. 1984 [9]	ASS	20	Arthritis	50	
Oddis et al. 1990 [10]	ASS	21	Arthritis	57	
Marguerie et al. 1990 [11]	ASS	29	Arthritis	33	
Love et al. 1991 [6]	IIM (total)	153	Arthritis	44	
	PM	48		54	
	DM	70		55	
	CAM	12		8	
	IBM	23		9	
Citera et al. 1994 [4]	IIM	29	Arthritis	27.5	
Tanimoto et al.1995 [7]	IIM	335	Arthritis/arthralgia	48.7	
Troyanov et al. 2005 [12]	IIM+OvL	100	Arthritis	34	40 (8.7)
	PM	33		33	36
	DM	30		14	17
Hervier et al. 2012 [13]	ASS	233	Polyarthritis	20	
Klein et al. 2014 [5]	IIM	106	Arthritis	37	53 (6.1)
	PM	46		41	59
	DM	40		38	55
	CAM	8		13	25
	IMNM	11		13	36
	IBM	1		100	100
Cavagna et al. 2015 [14•]	ASS	225	Arthritis	64.5	76.5 (6.6)
Lefevre et al. 2015 [15]	ASS	45	Arthritis	27[a]	
Trallero-Araguas et al. 2016 [16]	ASS	147	Arthritis		70.1
Pinal-Fernadez et al. 2017 [17•]	ASS	169	Arthritis	19	50 (4.1)
Cavagna et al. 2017 [18]	ASS anti-Jo-1+	243	Arthritis	24[a]	
Lilleker et al. 2018[b] [19]	IIM	2288[b]	Arthritis		28
	DM				20
	PM				20
	ASS				50
	OvL				42
	IBM				8
	IMNM				10
	JDM				23
Casal-Dominguez et al. 2019 [8]	DM	178	Arthritis	6	18 (4.2)
	IIM anti-U1-RNP+	20	Arthritis	15	60 (6.4)
	IMNM	135	Arthritis	1	1 (4.0)
	ASS	132	Arthritis	20	55 (4.7)
Nuño-Nuño et al. 2019 [20]	PM	136	Arthritis		34.6 (5.9)
	DM	104	Arthritis		48.1 (9.1)

Studies including more than 20 patients are shown only. *ASS*, antisynthetase syndrome; *IIM*, idiopathic inflammatory myopathy; *PM*, polymyositis; *DM*, dermatomyositis; *CAM*, cancer-associated myositis; *IBM*, inclusion body myositis; *IMNM*, immune-mediated necrotizing myopathy; *OvL*, overlap syndrome; *JDM*, juvenile dermatomyositis

[a] Arthritis as the first manifestation

[b] Data obtained from registry

simultaneously fulfilled criteria for other connective tissue disease had the highest prevalence of arthritis (64%), after exclusion of this patients' subgroup, still, 67 subjects (44%) had arthritis attributable to IIM. The lowest prevalence was seen in cancer-associated myositis (CAM) (8%) and inclusion body myositis (9%), whereas the frequencies in polymyositis (PM) (54%) and dermatomyositis (DM) (55%) were almost equal. Arthritis was present in 8 out of 29 PM/DM patients from Argentina (27.5%) [4]. There were significantly more males among patients with arthritis (75%) compared with those without arthritis (19%). Prevalence of arthritis in a separately analyzed group of 14 patients with an overlap syndrome was 79%. Non-erosive arthritis or arthralgias were documented in 163 out of 335 patients (49%) from a Japanese cohort used for development of PM/DM classification criteria [7]. However, the frequency of true arthritis in this study is probably overestimated due to inclusion of patients with arthralgias. In a Canadian group of 100 patients with IIM, 34 individuals presented with arthritis at the onset of disease and 40 had arthritis at the last follow-up [12]. Arthritis was most frequent among patients who had myositis as a manifestation of another CTD (58–68%), followed by PM (33–36%) and DM (13–17%) patients. In our cohort of 106 patients with IIM, a combination of patients' medical history and cross-sectional physical examination revealed that prevalence of arthritis at any time during the disease course had been 53% [5]. Arthritis was more common in PM (59%) and DM (55%) than in patients with CAM (25%) and immune-mediated necrotizing myopathy (IMNM) (36%). In 23 patients (22%), joint symptoms preceded muscle weakness and 16 (15%) patients had concurrent onset of arthritis and muscle weakness.

In the two most recent studies, each shows different prevalence of arthritis. The first one reports arthritis to be present in 11/178 (6%) dermatomyositis patients at the onset of the disease and cumulative prevalence of 18% after the follow-up of 4–6 years compared with 15% and 60% in myositis patients with anti-U1-RNP antibodies [8]. In a retrospective analysis of REMICAM registry, prevalence of arthritis was 35% (47/136) in patients with PM and 48% (50/104) in patients with DM [20].

Characteristics of Joint Involvement

In the cross-sectional analysis of our cohort [5], prevalence of arthritis at the time of physical examination was 49%. Polyarthritis was present in 25 patients (48%), and oligoarthritis and monoarthritis in 17 (33%) and 10 (19%) individuals, respectively (Fig. 1). In general, the most often affected joints were wrists (n = 23), followed by metacarpophalangeal joints (MCP), proximal interphalangeal joints (PIP) and shoulders (n = 22). Elbows (n = 14), acromioclavicular joints, ankles, and tarsal joints (n = 13), metatarsophalangeal (MTP) joints, and knees [11 and 10] were affected less frequently. Involvement of temporomandibular, sternoclavicular, and distal interphalangeal joints (DIP) and PIP joints of the feet and hips was also observed. Symmetrical polyarthritis in a subgroup of 39 patients with arthritis at disease onset was a most common pattern (85%), followed by oligoarthritis (13%), and monoarthritis (3%). We did not find any difference in the prevalence of arthritis among individual IIM subgroups. Some IIM patients had joint deformities similar to those seen in RA (Fig. 2). X-rays of peripheral joints were available for evaluation in 47 patients. Joint erosions were present only in two cases: in a patient with an overlap of PM with rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA) positive RA, and in a patient with anti-Jo-1 positive antisynthetase syndrome with DM-like rash. Joint involvement in IIM is usually described as a non-erosive oligo- or polyarthritis [21]. In previously mentioned small cohort from Argentina, 5 patients presented with oligoarthritis and 3 with polyarthritis. The most frequently affected joints were PIP of the hands and knees in 5 cases, followed by MCP in 2 and DIP joints, wrists, ankles, and elbows in one patient. Arthritis was temporarily associated with muscle involvement in all patients but one, in whom joint inflammation preceded the remaining symptomatology by 3 months. No patient had erosive or destructive changes on X-ray; in two of them, soft tissue swelling was seen [4].

Presence of non-erosive [22–24], erosive [25], and even destructive polyarthritis [26–28] was documented in several case reports. Destructive joint involvement is usually seen in patients with an overlap with ACPA and/or RF positive RA. However, presence of erosions on X-ray was observed in 12% of patients with ASS in an Italian cohort [29•].

In a recent retrospective evaluation of ultrasonographic findings in 8 patients with ASS [30], synovial hypertrophy was present in all, and Doppler signal activity, corresponding to active inflammation, was detected in 13 out of total 17 joints/regions examined (76%). Effusion was present in 72% (n = 12) of symptomatic joints. In five patients (63%), joint erosion or joint surface irregularities were seen. Marked tenosynovitis was found in the finger flexors or wrist extensor tendons in 7 patients.

In a cross-sectional study, we have performed ultrasonographic examination of 54 randomly selected patients with IIM treated at our institution [31]. A positive control group consisted of 60 patients with RA. Ultrasonographic joint assessment was performed using US-7 score [32] which evaluates unilateral synovitis, tenosynovitis and bone erosions in wrist, MCP 2, 3, hand PIP 2, 3, and MTP 2, 5 joints. The side with more severe clinical involvement, or the dominant side, if both sides involved equally, was scored. Both Grey-Scale (GS) and PowerDoppler (PD) were used to grade synovitis and tenosynovitis. Total US-7 score was significantly lower in IIM patients compared with RA controls. Similarly, GS and PD synovitis, and GS and PD tenosynovitis, as well as erosion partial scores

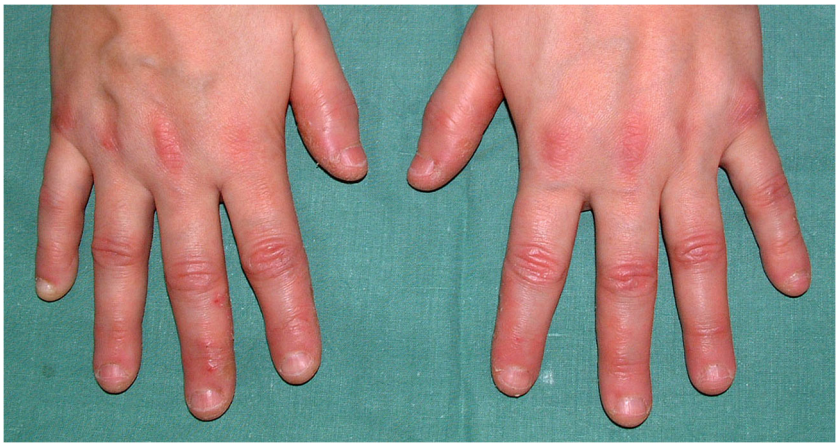

Fig. 1 Polyarthritis in a patient with antisynthetase syndrome involving mainly PIP and MCP joints, as well as IP joints of the thumbs. Note the presence of mechanic's hands

were also significantly lower in IIM. However, when individuals with negative findings were excluded from the analysis and only patients with quantifiable synovitis were taken into account, no difference in the total US-7 PD synovitis score between IIM and RA was found. With the exception of wrists, there was no difference between IIM and RA in the severity of involvement in the MCP, PIP, and MTP joints with quantifiable synovitis. These results suggest that joint involvement detectable by ultrasonography is frequent in patients with myositis. The most common finding in IIM is active synovitis; tenosynovitis and bone erosions are rare. Compared with RA, the arthritis in IIM is admittedly less frequent; however, when present, the activity of synovitis is similar.

A specific joint involvement caused by IIM, particularly in patients with ASS, is subluxing arthropathy—an extreme joint instability, first described by Bunch [33] in the interphalangeal joint of the thumb ("floppy finger") (Fig. 3). It has been reported in numerous papers since and the association with antisynthetase autoantibodies, predominantly anti-Jo-1, was described [5, 10, 34, 35]. The subluxation was associated with peri- and intra-articular calcinosis in some reports [35, 36]. Different joints may be affected with subluxing arthropathy, but the most frequent sites are wrists, and MCP, PIP, and DIP joints of the hands [34] (video).

The importance of joint involvement and arthritis activity for patients with IIM has been rarely evaluated. We used visual analogue scales (VAS 0-100 mm) to assess arthritis activity and joint damage both by patients and physician (MD) [5]. In patients with any joint involvement, the median MD-assessed activity was 19.4 ± 20.5, self-assessed activity was 26.5 ± 23.4, and MD-assessed joint damage was 21.2 ± 22.8. The contribution of arthritis to the overall morbidity was reported to be small, moderate, and large by 22.6%, 8.5%, and 6.6% patients, respectively. When joint disease was considered as a proportion of total morbidity on a semiquantitative scale, 62% of patients felt that arthritis did not play any role in the overall disease burden. However, in some patients, arthritis contributed significantly to the overall morbidity. Seven out of 56 patients reported that arthritis was very significant and in 2, the total disease burden was driven mostly by joint involvement. In addition, relapses of the disease were associated with arthritis in almost half of the patients. Thus, in some patients, arthritis may be the predominant symptom of IIM.

Autoantibody Association

It has been shown that myositis-specific antibodies (MSA) are associated with characteristic phenotypes of IIM. Although arthritis may be present in patients with all MSAs, it affects mostly those with antibodies against aminoacyl-tRNA synthetases (antisynthetase, ARS). Antibodies against eight ARSs have been described so far (Jo-1, PL-7, PL-12, EJ, OJ, KS, Zo, Ha), with anti-Jo-1 antibody being the most common of all MSAs [37•].

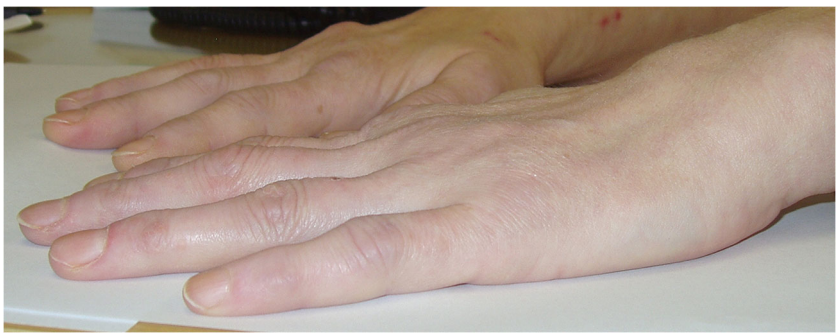

Fig. 2 Chronic polyarthritis in a patient with anti-Jo-1-positive antisynthetase syndrome showing similar deformities to those seen in rheumatoid arthritis

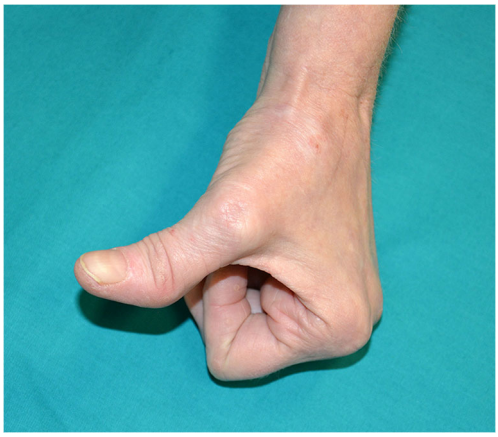

Fig. 3 An example of subluxing arthropathy of the thumb in a patient with antisynthetase syndrome

Significantly, higher prevalence of arthritis in ARS-positive patients in comparison with anti-Mi-2 positive, anti-SRP positive, and MSA negative patients was reported in Love's cohort [6]. In another report, 366 (82%) patients with arthritis were anti-Jo-1 positive and 78 (18%) had another ARS (33 patients (42%) were anti-PL-7, 29 were (37%) anti-PL-12, 9 were (11%) anti-EJ, and 4 were (5%) anti-OJ positive). In addition, 4 patients (5%) were double positive (1 OJ/EJ and 3 PL-7/PL-12) [29•]. In our study, we found out that arthritis was present at some point in 27 out of 29 anti-Jo-1 positive patients, prevalence significantly higher compared with patients without anti-Jo-1 antibodies (29 out of 77) [5]. Interestingly, anti-MDA5 antibody–positive patients can have a phenotype similar to that of the antisynthetase syndrome. In a study from Johns Hopkins, anti-MDA5 antibody–positive patients had higher prevalence of mechanics hands, fevers, and inflammatory arthritis in comparison with anti-MDA5-negative patients (81.8% vs. 26.7%) [38•]. Arthritis in the anti-MDA5-positive patients was frequently symmetric, affecting small joints of the hands and was associated with morning stiffness, a pattern similar to RA. A small erosion on the radial site of the 2nd metacarpal head only detectable by MRI was reported in one patient. Conventional X-rays did not demonstrate erosive disease in any of the patients with arthritis. An example of arthritis in anti-MDA5 positive patient is shown in Fig. 4. Arthritis on physical examination was found in 46% of patients with anti-PM/Scl antibodies, frequency almost approaching antisynthetase syndrome and higher than prevalence of arthritis in patients with DM or IMNM in a recently published cohort of patients from the NIH [39]. Although patients positive for both anti-PM/Scl-75 and anti-PM/Scl-100 generally had very similar phenotypes and disease severity compared with those positive for just one of these autoantibodies, arthritis was significantly less frequent in those with double (5%) compared with single positivity (75% and 57%).

Arthritis in Antisynthetase Syndrome

Arthritis is a defining feature of the antisynthetase syndrome together with myositis, mechanic's hands, interstitial lung disease (ILD), fever, and Raynaud's phenomenon (RP) [40]. In historical cohorts (1983–1998), the prevalence of arthritis in patient with ASS was reported to be around 70% (33–100%) [41] (Table 1). Prevalence of arthritis in ASS in recent studies ranged from 20% (47/233) [13] to 50% (84/169) [17•] and 55% (72/132) [8] in US cohorts and was reported to be 70% in Spanish (103/147) [16] and Italian patients (445/636) [29•]. Two multi-centric studies of the AENEAS (American, European NEtwork of Antisynthetase Syndrome) collaborative group focused on anti-Jo-1-positive patients with ASS. In the first one, arthritis at disease onset was present in 144 out of 225 patients (65%). Arthritis was polyarticular and symmetrical in the majority of cases (67%) while the remaining patients had oligoarticular and/or asymmetrical arthritis. At the end of the follow-up, (median 80 months) arthritis at some point was documented in 172 patients (77%) and the proportion of polyarticular involvement did not change. Erosive changes were present in 22% of 167 patients with radiographs available [14•]. IgM-RF was positive in 53% of patients with erosive disease, and ACPA in 28%. In the second AENEAS study, 58 anti-Jo-1-positive individuals with arthritis without myositis or ILD at presentation were included. Arthritis was polyarticular in majority of patients (71%). IgM-RF was positive in 22 out of 57 (39%) and ACPA in 13 out of 47 (28%) patients assessed. Forty-one patients (71%) met the 1987 revised ACR classification criteria for RA. At the end of the follow-up (median 84 months), erosions were found in 35% of 20 patients with available radiographs of the hands. Thirty-eight patients (66%) developed myositis and 48 (83%) developed ILD during follow-up. The median lag between arthritis and myositis onset was 17 months [18]. The authors stress that underlying ASS should be considered in all patients presenting with arthritis, myositis, and ILD even if these are isolated manifestations. Similar observation was reported in a multicentre French cohort of 40 patients with ASS and joint symptoms; 27% of which presented with isolated polyarthritis [15]. Patients with isolated arthritis at disease onset had a lower overall frequency of pulmonary and muscle symptoms with significantly delayed onset. When present (32%), Raynaud's phenomenon was the earliest non-articular manifestation of ASS. Therefore, particularly in patients with seronegative RA-like polyarthritis and RP, the possibility of underlying ASS should be considered.

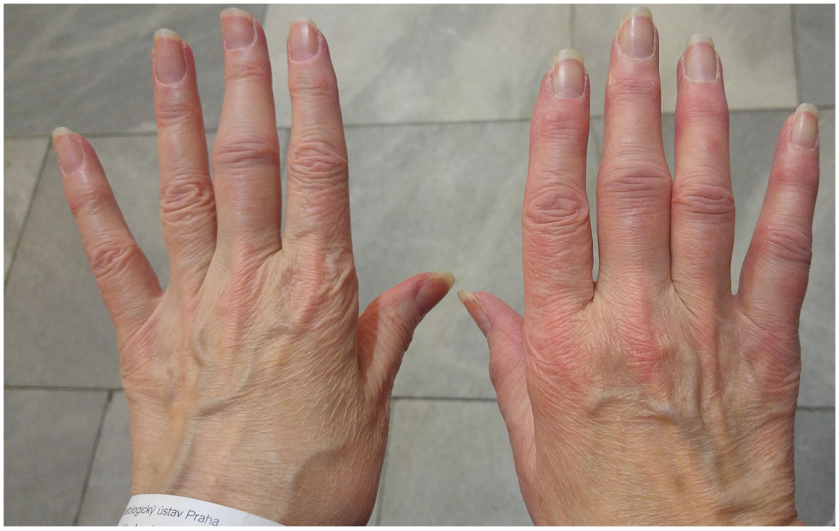

Fig. 4 Symmetrical arthritis in a female anti-MDA5-positive patient with hypomyopathic DM, particularly obvious in PIP joints of the 3rd fingers

Overlap with Rheumatoid Arthritis

Overlap syndrome of myositis and RA is occasionally documented in the literature. The term "overlap myositis" defining the situation when patient fulfils classification criteria of both IIM and other connective tissue disease (CTD) is often used inconsistently and some authors define overlap myositis as myositis plus one or more other symptoms without meeting criteria for other CTD [12, 20]. "True overlap", e.g., fulfilment of classification criteria of both IIM (any, but most often the classical criteria of Bohan and Peter [42, 43]) and RA (either ACR 1987 [44] or ACR/EULAR 2010 [45]), was documented in 4–8% patients with IIM [20, 46]. In older and smaller studies, no such patients were identified [47, 48]. The reported prevalence of RF and/or ACPA positivity among IIM patients is slightly elevated: 12% [46], 13% [47], and 14% [48]. Slightly higher or similar proportions were observed in anti-Jo-1-positive patients with ASS with IgM-RF and ACPA positivity in 22% and 10%, respectively. Both RF and ACPA positivity was higher in IIM patients with arthritis (32% and 14% versus 8% and 2%, respectively) [14•]. The prevalence of IgM-RF and ACPA positivity in the second AENEAS study described above was even higher (39% and 28%, respectively). Interestingly, all patients with polyarticular arthritis also met the ACR 1987 criteria for RA [18].

When 228 Japanese patients with rheumatoid arthritis, 25% of which had concurrent interstitial lung disease, were tested for the presence of ARS, 14 (6%) cases yielded positive results. Six of these patients had anti-PL-7 antibodies, four anti-EJ antibodies, two had anti-PL-12 antibodies, one had anti-OJ antibodies, and one had anti-Jo-1 antibodies. ILD complications were significantly more common among anti-ARS antibody–positive patients and authors recommend that RA patients, especially those with ILD complications, should be tested for anti-ARS antibodies. This study, however, did not focus on myopathy or characteristics of arthritis in anti-ARS-positive patients [49].

Anti-TNF-Induced Myositis in Patients Treated for Arthritis

A specific albeit rare situation is new onset of myositis in patients treated with tumor necrosis factor inhibitors (TNFi) for another autoimmune disease. TNFi are commonly used in the treatment of RA, axial spondyloarthritis (axSpA), psoriatic arthritis (PsA), and idiopathic bowel disease (IBD) [50]. Efficacy of TNFi in the treatment of IIM has not been conclusively established [51]. So far, 29 cases of new onset myositis in patients on TNFi therapy were reported [52–57]. The primary diagnosis requiring TNFi therapy was RA in 21 cases; the rest of the patients were treated for axSpA in three cases, and for PsA, psoriasis, IBD, juvenile idiopathic arthritis, and sarcoidosis each in one case. Several TNFi have been implicated in the development of myositis, (10 RA patients were treated with etanercept, 7 with adalimumab, and 3 received infliximab, various TNFi were used for treatment of other diagnoses). A majority of patients developed anti-Jo-1 autoantibodies—they were detected in 11 cases; three other patients developed ANA, two anti-PL-12 and single patients were tested positive for PM-Scl, PL-7, U1-RNP, and MDA5 antibodies. One patient was reported as anti-Jo-1 negative, four as negative for all MSAs. No data regarding autoantibody profile were available in three cases. Myositis significantly improved or at least responded in all patients after cessation of TNFi and with immunosuppressive treatment [52–57]. It is feasible that at least some of these patients had IIM from the beginning and were initially misdiagnosed as having RA.

Conclusions

Based on reviewed data, arthritis, or joint involvement in general, is a common symptom of IIM, affecting from one-fifth to

one-half of the patients with myositis. Arthritis is more frequent in patients with ASS, with reported prevalence between 50 and 75%. Apart from higher prevalence, the arthritis in ASS is more often erosive. The most typical joint involvement in IMM is symmetrical non-erosive polyarthritis affecting small joints of the hands similar to RA. Other joints can be involved as well, albeit less frequently. There is a strong association of arthritis with antisynthetase autoantibodies, especially with anti-Jo-1. Overlap of IIM and RA is infrequent, but double positivity for myositis-specific autoantibody, mainly anti-Jo-1 and RF and/or ACPA, has been reported. Arthritis is the first manifestation in a substantial number of IIM patients and may be misdiagnosed as RA. Therefore, in seronegative RA patients with ILD or RP, the possibility of IMM and ASS in particular should be considered in differential diagnosis.

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Compliance with Ethical Standards

Conflict of Interest Dr. Vencovsky reports grants from Czech Health Research Council and grants from Czech Ministery of Health, during the conduct of the study. Dr. Klein and Dr. Mann have nothing to disclose.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

(1•) Lundberg IE, de Visser M, Werth VP. Classification of myositis. Nat Rev Rheumatol. 2018;14(5):269–78 **A very useful review describing advances in the identification of clinical spectrum of idiopathic inflammatory myopathies and their associations with autoantibodies. Also mentioned is the use of the new EULAR–ACR classification criteria for adult and juvenile IIMs for capturing some disease subgroups.**

(2) Dalakas MC. Inflammatory muscle diseases. N Engl J Med. 2015;372(18):1734–47.

(3) Gunawardena H. The clinical features of myositis-associated autoantibodies: a review. Clin Rev Allergy Immunol. 2017;52(1): 45–57.

(4) Citera G, Goni MA, Maldonado Cocco JA, Scheines EJ. Joint involvement in polymyositis/dermatomyositis. Clin Rheumatol. 1994;13(1):70–4.

(5) Klein M, Mann H, Plestilova L, Betteridge Z, McHugh N, Remakova M, et al. Arthritis in idiopathic inflammatory myopathy: clinical features and autoantibody associations. J Rheumatol. 2014;41(6):1133–9.

(6) Love LA, Leff RL, Fraser DD, Targoff IN, Dalakas M, Plotz PH, et al. A new approach to the classification of idiopathic inflammatory myopathy: myositis-specific autoantibodies define useful homogeneous patient groups. Medicine (Baltimore). 1991;70(6): 360–74.

(7) Tanimoto K, Nakano K, Kano S, Mori S, Ueki H, Nishitani H, et al. Classification criteria for polymyositis and dermatomyositis. J Rheumatol. 1995;22(4):668–74.

(8) Casal-Dominguez M, Pinal-Fernandez I, Corse AM, Paik J, Albayda J, Casciola-Rosen L, et al. Muscular and extramuscular features of myositis patients with anti-U1-RNP autoantibodies. Neurology. 2019;92(13):e1416–e26.

(9) Bernstein RM, Morgan SH, Chapman J, Bunn CC, Mathews MB, Turner-Warwick M, et al. Anti-Jo-1 antibody: a marker for myositis with interstitial lung disease. Br Med J (Clin Res Ed). 1984;289(6438):151–2.

(10) Oddis CV, Medsger TA Jr, Cooperstein LA. A subluxing arthropathy associated with the anti-Jo-1 antibody in polymyositis/dermatomyositis. Arthritis Rheum. 1990;33(11):1640–5.

(11) Marguerie C, Bunn CC, Beynon HL, Bernstein RM, Hughes JM, So AK, et al. Polymyositis, pulmonary fibrosis and autoantibodies to aminoacyl-tRNA synthetase enzymes. Q J Med. 1990;77(282): 1019–38.

(12) Troyanov Y, Targoff IN, Tremblay JL, Goulet JR, Raymond Y, Senecal JL. Novel classification of idiopathic inflammatory myopathies based on overlap syndrome features and autoantibodies: analysis of 100 French Canadian patients. Medicine (Baltimore). 2005;84(4):231–49.

(13) Hervier B, Devilliers H, Stanciu R, Meyer A, Uzunhan Y, Masseau A, et al. Hierarchical cluster and survival analyses of antisynthetase syndrome: phenotype and outcome are correlated with anti-tRNA synthetase antibody specificity. Autoimmun Rev. 2012;12(2):210–7.

(14•) Cavagna L, Nuno L, Scire CA, Govoni M, Longo FJ, Franceschini F, et al. Clinical spectrum time course in anti Jo-1 positive antisynthetase syndrome: results from an international retrospective multicenter study. Medicine (Baltimore). 2015;94(32):e1144 **Two hundred and twenty five patients with anti-Jo-1 antibodies were evaluated for complete or incomplete manifestations of antisynthetase syndrome (ASS) at disease presentation. Around 80% had an incomplete form of ASS and from these 60% developed further features of ASS during follow-up, most frequently interstitial lung disease.**

(15) Lefevre G, Meyer A, Launay D, Machelart I, DeBandt M, Michaud J, et al. Seronegative polyarthritis revealing antisynthetase syndrome: a multicentre study of 40 patients. Rheumatology (Oxford). 2015;54(5):927–32.

(16) Trallero-Araguas E, Grau-Junyent JM, Labirua-Iturburu A, Garcia-Hernandez FJ, Monteagudo-Jimenez M, Fraile-Rodriguez G, et al. Clinical manifestations and long-term outcome of anti-Jo1 antisynthetase patients in a large cohort of Spanish patients from the GEAS-IIM group. Semin Arthritis Rheum. 2016;46(2):225–31.

(17•) Pinal-Fernandez I, Casal-Dominguez M, Huapaya JA, Albayda J, Paik JJ, Johnson C, et al. A longitudinal cohort study of the antisynthetase syndrome: increased severity of interstitial lung disease in black patients and patients with anti-PL7 and anti-PL12 autoantibodies. Rheumatology (Oxford). 2017;56(6):999–1007 **This study shows different associations of antisynthetase antibodies with muscular and pulmonary manifestations in patients with antisynthetase syndrome as well as more severe interstitial lung disease in black patients.**

(18) Cavagna L, Nuno L, Scire CA, Govoni M, Longo FJ, Franceschini F, et al. Serum Jo-1 autoantibody and isolated arthritis in the antisynthetase syndrome: review of the literature and report of the experience of AENEAS collaborative group. Clin Rev Allergy Immunol. 2017;52(1):71–80.

(19) Lilleker JB, Vencovsky J, Wang G, Wedderburn LR, Diederichsen LP, Schmidt J, et al. The EuroMyositis registry: an international collaborative tool to facilitate myositis research. Ann Rheum Dis. 2018;77(1):30–9.

(20) Nuno-Nuno L, Joven BE, Carreira PE, Maldonado-Romero V, Larena-Grijalba C, Llorente Cubas I, et al. Overlap myositis, a distinct entity beyond primary inflammatory myositis: a retrospective analysis of a large cohort from the REMICAM registry. Int J Rheum Dis. 2019;22(8):1393–401.

(21) Hochberg MC. Rheumatology. 7th edition ed: Elsevier p1838.

(22) Goussot R, Theulin A, Goetz J, Sibilia J, Gottenberg JE, Meyer A. An arthro-dermato-pulmonary syndrome associated with anti-MDA5 antibodies. Joint Bone Spine. 2014;81(3):266.

(23) Ozturk MA, Unverdi S, Goker B, Haznedaroglu S, Tunc L. A patient with antisynthetase syndrome associated with deforming arthritis and periarticular calcinosis sine myositis. Scand J Rheumatol. 2007;36(3):239–41.

(24) Schedel J, Butz B, Volk M, Feuerbach S, Scholmerich J, Muller-Ladner U, et al. Nonerosive metacarpophalangeal arthritides in a patient with dermatomyositis. J Rheumatol. 2004;31(7):1457–8.

(25) Wasko MC, Carlson GW, Tomaino MM, Oddis CV. Dermatomyositis with erosive arthropathy: association with the anti-PL-7 antibody. J Rheumatol. 1999;26(12):2693–4.

(26) Nagashima T, Sato H, Minota S. Destructive arthropathy associated with dermatomyositis sine myositis positive for anti-Jo-1 and anti-cyclic citrullinated peptide antibodies. J Rheumatol. 2009;36(9):2133–4.

(27) Tomioka H, Kaneko M, Kogata Y, Katsuyama E, Ishikawa S, Fujii T. Case of interstitial lung disease with anti-EJ and anti-CCP antibodies preceding rheumatoid arthritis. Respir Investig. 2012;50(2):66–9.

(28) Lee LH, Srikanth A, Gupta A. Calcinosis and rapidly destructive arthropathy associated with anti-jo1 antibody. J Rheumatol. 2015;42(3):547–8.

(29•) Gonzalez-Gay MA, Montecucco C, Selva-O'Callaghan A, Trallero-Araguas E, Molberg O, Andersson H, et al. Timing of onset affects arthritis presentation pattern in antisyntethase syndrome. Clin Exp Rheumatol. 2018;36(1):44–9 **In this retrospective large international cohort of patients with antisynthetase antibodies, 70% (445 patients) had arthritis. Analysis of presentation pattern showed that arthritis at disease onset had more frequently RA-like features and arthritis appearing later during the disease course was more similar to the type seen in other connective tissue diseases.**

(30) Miller JB, Danoff SK, Bingham CO 3rd, Paik JJ, Mecoli CA, Tiniakou E, et al. Sonographic findings from inflammatory arthritis due to antisynthetase syndrome. Clin Rheumatol. 2019;38(5):1477–83.

(31) Klein M, Mann H, Hanova P, Plestilova L, Zavada J, Remakova M, et al. Clinical and Ultrasonographic Characteristics of arthritis in patients with idiopathic inflammatory myopathies. Ann. Rheum. Dis. 2019;72(Sppl.3):A644–A645..

(32) Backhaus M, Ohrndorf S, Kellner H, Strunk J, Backhaus TM, Hartung W, et al. Evaluation of a novel 7-joint ultrasound score in daily rheumatologic practice: a pilot project. Arthritis Rheum. 2009;61(9):1194–201.

(33) Bunch TW, O'Duffy JD, McLeod RA. Deforming arthritis of the hands in polymyositis. Arthritis Rheum. 1976;19(2):243–8.

(34) Meyer O, Charlanne H, Cherin P, Allanore Y, Coquerelle P, Grardel B, et al. Inflammation. Subluxing arthropathy: an unusual manifestation of the antisynthetase syndrome. Ann Rheum Dis. 2009;68(1):152–3.

(35) Queiro-Silva R, Banegil I, de Dios-Jimenez de Aberasturi JR, Belzunegui-Otano J, Gonzalez-Beneitez C, Figueroa-Pedrosa M. Periarticular calcinosis associated with anti-Jo-1 antibodies sine myositis. Expanding the clinical spectrum of the antisynthetase syndrome. J Rheumatol. 2001;28(6):1401–4.

(36) Delbrel X, Schaeverbeke T, Lifermann F, Dehais J. Arthropathy associated with anti-Jo-1 antibody. Joint Bone Spine. 2001;68(2):166–9.

(37•) McHugh NJ, Tansley SL. Autoantibodies in myositis. Nat Rev Rheumatol. 2018;14(5):290–302 **A very informative review on myositis-specific autoantibodies and myositis-associated autoantibodies and their relation to disease subgroups, muscular and extramuscular manifestations.**

(38•) Hall JC, Casciola-Rosen L, Samedy LA, Werner J, Owoyemi K, Danoff SK, et al. Anti-melanoma differentiation-associated protein 5-associated dermatomyositis: expanding the clinical spectrum. Arthritis Care Res. 2013;65(8):1307–15 **This paper describes similarities between anti-MDA5-positive patients and antisynthetase syndrome, including presence of arthritis.**

(39) De Lorenzo R, Pinal-Fernandez I, Huang W, Albayda J, Tiniakou E, Johnson C, et al. Muscular and extramuscular clinical features of patients with anti-PM/Scl autoantibodies. Neurology. 2018;90(23):e2068–e76.

(40) Mahler M, Miller FW, Fritzler MJ. Idiopathic inflammatory myopathies and the anti-synthetase syndrome: a comprehensive review. Autoimmun Rev. 2014;13(4-5):367–71.

(41) Imbert-Masseau A, Hamidou M, Agard C, Grolleau JY, Cherin P. Antisynthetase syndrome. Joint Bone Spine. 2003;70(3):161–8.

(42) Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). N Engl J Med. 1975;292(7):344–7.

(43) Bohan A, Peter JB. Polymyositis and dermatomyositis (second of two parts). N Engl J Med. 1975;292(8):403–7.

(44) Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31(3):315–24.

(45) Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2010;69(9):1580–8.

(46) Ide V, Bossuyt X, Blockmans D, De Langhe E. Prevalence and clinical correlates of rheumatoid factor and anticitrullinated protein antibodies in patients with idiopathic inflammatory myopathy. RMD Open. 2018;4(2):e000661.

(47) Labrador-Horrillo M, Martinez MA, Selva-O'Callaghan A, Delgado JF, Martinez-Gomez X, Trallero-Araguas E, et al. Anticyclic citrullinated peptide and anti-keratin antibodies in patients with idiopathic inflammatory myopathy. Rheumatology (Oxford). 2009;48(6):676–9.

(48) Takasaki Y, Yamanaka K, Takasaki C, Matsushita M, Yamada H, Nawata M, et al. Anticyclic citrullinated peptide antibodies in patients with mixed connective tissue disease. Mod Rheumatol. 2004;14(5):367–75.

(49) Matsushita M, Tamura N, Ogasawara M, Tada K, Yamaji K, Takasaki Y. The association of anti-aminoacyl-transfer ribonucleic acid synthetase antibodies in patients with rheumatoid arthritis and interstitial lung disease. Arch Rheumatol. 2018;33(1):26–32.

(50) Reimold AM. New indications for treatment of chronic inflammation by TNF-alpha blockade. Am J Med Sci. 2003;325(2):75–92.

(51) Albayda J, Christopher-Stine L. Novel approaches in the treatment of myositis and myopathies. Ther Adv Musculoskelet Dis. 2012;4(5):369–77.

(52) Dicaro D, Bowen C, Dalton SR. Dermatomyositis associated with anti-tumor necrosis factor therapy in a patient with psoriasis. J Am Acad Dermatol. 2014;70(3):e64–5.

(53) Kato M, Oiso N, Nozaki Y, Inoue A, Hosono Y, Funauchi M, et al. Antitumor necrosis factor alpha inhibitor-induced dermatomyositis and interstitial lung disease with anti-PL12 autoantibody: signs of antisynthetase syndrome. J Dermatol. 2014;41(11):1034–6.

(54) Takata M, Yamasaki A, Yamada N, Hagino H, Funaki Y, Harada T, et al. A case of clinically amyopathic dermatomyositis that developed during anti-TNF-alpha therapy for rheumatoid arthritis. Allergol Int. 2018;67(2):286–8.

(55) Tariq H, Ayesha B, Weidenheim K, Franchin G. Etanercept-induced myositis: do we have to stop it? A surprising outcome. BMJ Case Rep. 2016;2016:bcr2015213577.

(56) Zengin O, Onder ME, Alkan S, Kimyon G, Huseynova N, Demir ZH, et al. Three cases of anti-TNF induced myositis and literature review. Rev Bras Reumatol Engl Ed. 2017;57(6):590–5.

(57) Zhou Y, Lower EE, Li H, Baughman RP. Sarcoidosis patient with lupus pernio and infliximab-induced myositis: response to Acthar gel. Respir Med Case Rep. 2016;17:5–7.