Original Article

Articular manifestations in Japanese patients with polymyositis and dermatomyositis

Takao Nagashima[1], Takamasa Murosaki[1], Kyoko Honne[1], Yasuyuki Kamata[1], Katsuya Nagatani[1], Masahiro Iwamoto[1], and Seiji Minota[1]

[1]Division of Rheumatology and Clinical Immunology, Department of Medicine, Jichi Medical University, Yakushiji 3311-1, Shimotsuke, Tochigi, 329-0498, Japan.

Abstract

Objective：To investigate the association between joint symptoms and related conditions in Japanese patients with polymyositis（PM）and dermatomyositis（DM）.
Methods：We retrospectively reviewed all patients with PM/DM who were admitted to our department from January 2007 to March 2012. Clinical data on these patients were retrieved from the medical records.
Results：Seventy-eight patients（20 with PM and 58 with DM）were enrolled. Among them, 37 patients（47%）had arthralgia or arthritis. Joint symptoms were more frequent in DM than PM（53% vs. 30%, *P*=0.07）. Anti-aminoacyl tRNA antibodies（ASA）were positive in 25 patients（32%）, and anti-cyclic citrullinated peptide（CCP）antibody was positive in 7 patients（9%）. Patients with anti-Jo-1 antibody had a high frequency of polyarthritis（82%）, while anti-CCP antibody was positive in 4 out of 11 patients with anti-Jo-1 antibody（36%）. Among patients with joint symptoms, anti-Jo-1 antibody was positive in 67% of the patients with PM, but was positive in only 16% of the patients with DM. Four of the 78 patients（5%）were initially diagnosed and treated as having rheumatoid arthritis. Multivariate analysis showed that fever, Raynaud's phenomenon, and anti-Jo-1 antibody were associated with joint symptoms, whereas overall ASA positivity showed no significant difference between patients with or without joint symptoms.
Conclusion：Forty-seven percent of patients with PM/DM had joint symptoms. Except for anti-Jo-1 antibody, ASA were not associated with joint symptoms in Japanese PM/DM patients.
（Key words：anti-cyclic citrullinated peptide antibody, antisynthetase syndrome, dermatomyositis, polymyositis, rheumatoid arthritis.）

Introduction

Polymyositis（PM）and dermatomyositis（DM）are immune-mediated disorders characterized by inflammation of the skeletal muscles. Joint manifestations are common in patients with PM/DM, and about 20 to 49% of them have arthralgia or arthritis[1-5]. Typically, they develop arthralgia or nonerosive arthritis, which is often only seen at the onset of myositis. However, a few patients develop deforming, subluxing, erosive, and destructive arthritis or periarticular calcification, and these rare manifestations have been documented in a case report and a small case series[1, 6-9].

Joint manifestations are often seen in patients who are positive for anti-aminoacyl tRNA synthetase antibodies（ASA）[5]. Anti-histidyl tRNA synthetase antibody（anti-Jo-1 antibody）is the most common of the ASA and 15-25% of patients with PM/DM are positive for this antibody[10, 11]. Patients with ASA show a distinct clinical profile that includes myositis, fever, Raynaud's phenomenon, mechanic's hands, and interstitial lung disease（ILD）as well as joint symptoms. Patients with this constellation of symptoms and ASA positivity are occasionally classified as having "anti-synthetase syndrome". The prevalence of such symptoms differs slightly among each of the ASA. For example, anti-Jo-1 antibody is commonly associated with arthralgia/arthritis, myositis, and ILD, whereas patients with anti-PL-7 or anti-PL-12 antibody are less likely to develop arthralgia/arthritis and myositis[12].

Although joint manifestations are frequent in PM and

Correspondence to：Takao Nagashima., Division of Rheumatology and Clinical Immunology, Department of Medicine, Jichi Medical University, Yakushiji 3311-1, Shimotsuke, Tochigi, 329-0498, Japan. E-mail：naga4ma@jichi.ac.jp
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DM, the characteristics of Japanese patients who are likely to develop such symptoms have rarely been investigated. While the frequency of joint manifestations associated with each ASA has been reported[13], the patients did not necessarily satisfy the criteria for PM/DM. Moreover, anti-cyclic citrullinated peptide (CCP) antibody, which is a useful marker of rheumatoid arthritis (RA) and is associated with more erosive disease[14], has rarely been investigated in PM/DM patients with joint symptoms[15, 16]. In the present study, we retrospectively examined the frequency of joint symptoms in Japanese patients at the onset of PM/DM, and we investigated the association between joint manifestations and various factors including anti-CCP antibody.

Methods

All of the patients with PM and DM who were admitted to our department from January 2007 to March 2012 were retrospectively reviewed. Diagnosis of PM/DM was based on the Bohan and Peter criteria[17]. We excluded patients who only had ILD, fever, or arthritis along with ASA positivity (i.e., patients who did not satisfy the criteria for PM or DM).

Clinical features were retrospectively reviewed from the medical records. Fever was defined as an axillary temperature ≥38℃ during admission or measured by the patient before admission. The presence of arthritis/arthralgia was assessed by physical examination. ILD was diagnosed from the presence of interstitial changes on chest computed tomography (CT). Rapidly progressive-ILD was defined as progressive dyspnea or hypoxia with worsening of interstitial changes on chest CT scans within 1 month of the onset of respiratory manifestations. Radiographs of the joints were obtained at the attending physician's discretion.

The following laboratory tests were obtained at the first admission : C-reactive protein, (CRP), erythrocyte sedimentation rate (ESR), and serum levels of creatine kinase, lactate dehydrogenase, aldolase, KL-6, serum ferritin, anti-nuclear antibody (ANA), RAPA (rheumatoid arthritis particle agglutination), anti-CCP antibody, and ASA. RAPA and ANA were measured by our hospital laboratory, while anti-CCP and anti-Jo-1 were measured by SRL (Tokyo, Japan). Other ASA (excluding anti-Jo-1 antibody) and other myositis-associated antibodies were measured with line-blotting kits supplied by Euroimmun AG (Luebeck, Germany).

All patients were examined to detect underlying malignancy by appropriate methods (contrast-enhanced CT of the chest and abdomen, esophagogastroduodenoscopy, abdominal ultrasonography, fecal occult blood testing/colonoscopy, serum prostate specific antigen, mammography, and cervical smear). Cancer-associated myositis was diagnosed if a malignant tumor was detected within 3 years before or after the diagnosis of myositis. This retrospective study was approved by the Ethics committee of our hospital.

Statistical analysis

The chi-square test or Fisher's exact test was employed to compare categorical data between patients with and without joint manifestations, while the Mann-Whitney test or Student t-test was used for continuous variables. Multivariate logistic regression analysis was performed to examine the association of joint manifestations and various factors. Probability (P) values of less than 0.05 were considered significant. All analyses were performed using Microsoft Office Excel 2007 (Microsoft, Redmond, WA, USA) and JMP Statistical Package for Windows software, version 11 (SAS Institute Inc., Cary, NC, USA).

Results

During the study period, 80 patients were diagnosed as having PM or DM at our department. One Chinese patient and one Korean patient were excluded from this study. Among the remaining 78 patients, the diagnosis was PM in 20 patients and DM in 58 patients. The mean age (SD) was 57.0 (14.2) years, and 47 patients (60%) were women. Three patients showed overlap with SSc and 1 had overlap with SLE. Nine of the 78 patients (12%) had already been treated with glucocorticoids to control ILD, myositis, or arthritis before referral to our hospital. Nineteen patients (24%) had cancer-associated myositis, with the malignancy being gastric cancer in 6, colon cancer in 3, papillary thyroid cancer and lung cancer in 2, renal pelviureteral cancer in 2, and endometrial cancer and ovarian cancer in 1 patient each. Double cancer occurred in 2 patients (1 with thymic and colon cancer ; 1 with gastric and colon cancer).

Thirty-seven out of 78 patients (47%) had joint manifestations (6 with PM, 31 with DM). Joint symptoms were more frequent in patients with DM than in those with PM (53% vs. 30%, P=0.07). Polyarthritis was present in 18 patients (23%), while 19 patients only had arthralgia. Arthritis was limited to small joints (the proximal interphalangeal, metacarpophalangeal, and wrist joints) in 15 of the 18 patients with this symptom. With respect to arthralgia, larger joints (shoulders, elbows, knees, and ankles) were affected in 18 of the 19 patients and small joints were also involved in 6 patients. The clinical characteristics and laboratory findings of the patients with or without joint symptoms are compared in Table 1.

ASA were positive in 25 out of 78 patients (32%), but only 11 of these 25 patients (44%) had joint manifestations. The frequency of ANA, RF, and ASA positivity was not significantly different between patients with or without joint symptoms. Patients with anti-Jo-1 antibody had a high frequency of joint symptoms (82%). Anti-Jo-1 antibody was positive in 20% (4/20) of the patients with PM and 12%

Table 1. Comparison between patients with or without joint manifestations.

	arthritis/arthralgia (+) (n = 37)	arthritis/arthralgia (-) (n = 41)	univariate analysis *P value*	multivariate analysis *P value*	OR (CI)
Women, n	24 (65%)	23 (56%)	0.43		
Age, years (mean ± SD)	54.1 ± 16.1	59.7 ± 12.0	0.09		
DM, n	31 (84%)	27 (66%)	0.07		
ILD, n	26 (70%)	23 (56%)	0.2	0.19	0.433 (0.108–1.519)
RP-ILD, n	7 (19%)	8 (20%)	0.97		
Malignancy, n	6 (16%)	13 (32%)	0.11		
Clinical symptoms					
Fever (≥38°C), n	15 (41%)	8 (20%)	0.04*	0.018*	4.45 (1.387–20.231)
Mechanic's hands, n	9 (24%)	6 (15%)	0.28		
Raynaud's phenomenon, n	11 (30%)	3 (7%)	0.01*	0.004**	7.88 (1.863–44.825)
Gottron's sign (hands), n	20 (54%)	17 (41%)	0.27		
Gottron's sign (elbow, knee), n	24 (65%)	24 (59%)	0.57		
Hand edema, n	7 (19%)	4 (10%)	0.2		
Laboratory findings					
CK (IU/l)	1005 (162–2418)	1490 (333–4422)	0.21		
CK <300 IU/l, n	11 (30%)	9 (22%)	0.43		
LD (IU/l)	453 (359–573)	514 (310–855)	0.63		
Aldolase (U/l)	15.7 (8.6–30.4) (n = 32)	17.9 (7.6–49.0) (n = 32)	0.53		
Serum ferritin (ng/ml)	313 (114–861) (n = 31)	232 (110–506) (n = 34)	0.39		
KL-6 (U/ml)	570 (420–1008) (n = 33)	318 (220–622) (n = 37)	0.015*		
IgG (mg/dl)	1576 (1388–1724) (n = 35)	1396 (1181–1774) (n = 39)	0.11		
CRP (mg/dl)	0.5 (0.1–1.2)	0.3 (0.1–0.9)	0.71		
ESR (mm/h)	42 (25–71) (n = 33)	29 (18–39)	0.02*		
Autoantibodies					
ANA (≥40), n	22 (59%)	25 (61%)	0.89		
RAPA (≥40), n	32 (86%)	35 (85%)	0.89		
CCP, n	6 (16%)	1 (2%)	0.039*	0.107	6.15 (0.692–138.807)
Jo-1, n	9 (24%)	2 (5%)	0.015*	0.038*	6.5 (1.107–56.541)
PL-7, n	1 (3%)	6 (15%)	0.07		
PL-12, n	1 (3%)	1 (2%)	0.73		
EJ, n	0 (0%)	5 (12%)	0.035*		
ASA (total), n	11 (30%)	14 (34%)	0.68		
Mi-2, n	1 (3%)	2 (5%)	0.54		
SRP, n	1 (3%)	3 (7%)	0.35		
PM/Scl-75, n	0 (0%)	2 (5%)	0.27		
Ro-52, n	26 (70%)	21 (51%)	0.09		

Values are median (range) or number, except for age (mean ± SD).

ANA, antinuclear antibody; ASA, antisynthetase antibody; CADM, clinically amyopathic dermatomyositis; CCP, cyclic citrullinated peptide; CI, confidence interval; CK, creatine kinase; CRP, C-reactive protein; DM, dermatomyositis; ESR, erythrocyte sedimentation rate; ILD, interstitial lung disease; LD, lactate dehydrogenase; PM, polymyositis; RAPA, rheumatoid arthritis particle agglutination; RNP, ribonucleoprotein; RP-ILD, rapidly progressive-interstitial lung disease ; SRP, signal recognition particle. * $P < 0.05$, ** $P < 0.01$

Table 2. Clinical characteristics of the patients with positive anti-CCP antibody.

Patient	diagnosis	Age/ sex	Arthralgia/ arthritis	Fever	RP	Joint radiograph	ILD	autoantibody	ANA (×)	RAPA (×)	CCP (U/ml)
1	DM	48/M	arthralgia	No	No	n.d.	Yes	Jo-1	80	neg	12
2	DM, SSc	65/F	arthritis	Yes	No	n.d.	Yes	RNP	neg	640	18
3	DM, RA	48/F	arthritis	Yes	No	normal	Yes	Jo-1	neg	160	64
4	DM	60/F	arthralgia	Yes	No	n.d.	Yes	SSA	1280	1280	64
5	DM	59/F	No	No	No	n.d.	Yes	Jo-1	neg	40	58
6	CADM, RA	73/F	arthralgia	No	No	Carpal erosions	Yes	neg	320	neg	85
7	PM, RA	49/F	arthralgia	No	Yes	normal	Yes	Jo-1	40	40	35.4

ANA, antinuclear antibody; CADM, clinically amyopathic dermatomyositis; CCP, anti-cyclic citrullinated peptide antibody; DM, dermatomyositis; RA, rheumatoid arthritis; RAPA, rheumatoid arthritis particle agglutination; RNP, anti-ribonucleoprotein antibody; RP, Raynaud's phenomenon; SSc, systemic sclerosis; n.d., not done. Three patients who were diagnosed with RA have been reported previously (ref. 18).

(7/58) of those with DM. While anti-Jo-1 antibody was positive in 67% (4/6) of the PM patients with joint symptoms, it was only positive in 16% (5/31) of the DM patients with joint symptoms. According to univariate analysis, the factors associated with joint symptoms were fever, Raynaud's phenomenon, KL-6, ESR, anti-Jo-1 antibody, and anti-CCP antibody, while anti-EJ antibody was negatively associated with joint symptoms. Multivariate analysis identified fever, Raynaud's phenomenon, and anti-Jo-1 antibody as being associated with joint symptoms (P=0.018, 0.004, and 0.038, respectively). Comparison between the patients with or without polyarthritis (n=18 and 60, respectively) showed significant differences of age (P=0.029), ILD (P=0.007), fever (P<0.0005), Raynaud's phenomenon (P<0.0005), CK (P=0.006), CK <300 (P=0.037), and ESR (P=0.03), but there was no difference of anti-Jo-1 antibody (P=0.07) or anti-CCP antibody (P=0.5).

Arthritis preceded the onset of myositis in 6 out of 78 patients (8%). Four of them had previously been diagnosed with RA and 1 with Sjögren's syndrome (SS), after which these patients had been treated with conventional DMARDs and/or biological agents. The remaining 1 patient had been treated with prednisolone (5 mg/day) for unclassified arthritis. RF, anti-CCP, and anti-Jo-1 antibodies were each positive in 3 out of 6 patients, and anti-PL-12 antibody was also positive in 1 patient.

Demographic features of the 7 patients who were positive for anti-CCP antibody are shown in Table 2. All 7 patients had ILD. Four of them were also positive for anti-Jo-1 antibody. RA was diagnosed in 3 of them before the diagnosis of myositis. One patient had concomitant papillary thyroid cancer (patient No. 3), and one patient had gastric cancer 3 years before the diagnosis of DM (patient No. 4).

Hand radiographs showed abnormalities in 2 out of 21 patients who underwent radiological examination. In 1 patient, bilateral erosion of the carporadial joints was noted along with joint space narrowing. This patient was a 73-year-old woman with DM, in whom anti-CCP-positive RA had been diagnosed 1.8 years earlier, and her details have been reported previously[18]. In the other patient, narrowing of the right second metacarpophalangeal joint was seen without bone erosion. This patient was a 62-year-old woman in whom RA had been diagnosed by a local rheumatologist 6 months earlier, after which she had been treated with methotrexate and abatacept. Both anti-CCP and RF were positive (15.3 U/ml and 29 IU/ml, respectively) at the local hospital when RA was diagnosed. However, both of these antibodies were negative when DM was diagnosed 6 months later, probably because of treatment for RA.

Among the patients with cancer-associated myositis (n=19), 6 had joint symptoms. Arthritis was noted in 2 patients with anti-Jo-1 antibody, while the other 4 patients had arthralgia. The 2 patients with anti-Jo-1 antibody had early endometrial cancer and papillary thyroid cancer in 1 case each. A 45-year-old female PM with endometrial cancer underwent hysterectomy, but still required glucocorticoid treatment for myositis because it did not improve after surgery alone. Gottron's sign developed along with relapse of myositis at 3.5 years after the operation, so the diagnosis of PM was changed to DM. The other patient (patient No. 3 in Table 2) had papillary thyroid cancer, and a diagnosis of RA was made 1.5 years before the onset of DM[19].

Discussion

This retrospective study showed that 37 out of 78 patients with PM/DM (47%) had joint symptoms, a frequency consistent with that previously reported in Japan[4]. Joint symptoms were more frequent in DM than PM, although the difference was not significant. Anti-CCP antibody was positive in 7 patients (9%), and 4 out of 11 patients with anti-Jo-1 antibody also had anti-CCP antibody (36%). We found that anti-Jo-1 antibody was positive at a much higher frequency in PM patients with joint symptoms than in DM patients with joint symptoms, while overall ASA positivity did not differ between patients with or without joint symptoms.

DM patients tended to have more joint manifestations than PM patients. Although anti-Jo-1 antibody was associated with joint symptoms according to multivariate analysis, only 16% of DM patients with joint symptoms were positive for this antibody. In contrast, 67% of PM patients with joint symptoms showed anti-Jo-1 antibody positivity. Our findings suggest that anti-Jo-1 antibody is mainly associated with joint symptoms in PM patients, while other factors seem to be associated with joint symptoms in DM patients who are negative for this antibody.

The present study indicated that ASA were not associated with joint symptoms in Japanese PM/DM patients, a result that was inconsistent with previous reports[5, 20]. One of the reasons for this difference is that not all the joint symptoms of PM/DM are explained by ASA[21], since patients with other myositis-specific antibodies can also develop arthritis[22]. Second, only a few patients had ASA other than anti-Jo-1 antibody. Third, the clinical features associated with each type of ASA could differ between Japanese and Western patients[12, 13, 23], with Japanese patients being less likely to develop joint symptoms than Western patients[13].

Patients with anti-Jo-1 antibody can present with arthritis as their first manifestation. Arthritis preceded myositis or skin rash in 3 of 11 patients with anti-Jo-1 antibody (27%), 2 of whom had been diagnosed as RA[18]. This finding is consistent with a previous report that arthritis is the first symptom in 32% of patients with anti-Jo-1 antibody[24]. These patients may be diagnosed with RA, especially if ILD precedes myositis[21]. Actually, coexistence of RA and myositis is reported to be relatively frequent[18, 25, 26].

While only a few patients with PM/DM are positive for anti-CCP antibody, those patients often have joint symptoms and anti-CCP antibody can coexist with ASA. In the present study, 4 out of 11 patients with anti-Jo-1 antibody (36%) also had anti-CCP antibody. The reported frequency of anti-CCP positivity in patients with PM/DM varies from 13 to 30%[15, 27-30]. A high frequency of ASA has been reported in patients who have myositis overlapping with RA[25]. Anti-CCP antibody was reported to be positive in 29% of patients with ASA, and 21% had bone erosions or ankylosis on hand radiographs after a mean disease duration of 13.6 years[31]. Another study simultaneously detected anti-Jo-1 and anti-CCP antibodies in 2 out of 12 patients, and both of them had joint erosions[16]. In contrast, a study from Spain revealed that none of the PM/DM patients with anti-CCP antibody (13.3%) satisfied the ACR criteria for RA and none of them showed joint erosions on hand radiographs after a median disease duration of 6.2 years[15]. These contradictory radiographic findings may be due to differences of the observation period.

Several limitations of the present study must be addressed. First, not all of the patients with PM/DM who were referred to our hospital are comprehensively reviewed in our rheumatology department. Depending on the disease severity of skin, muscle, or lung, patients might be referred to the dermatology, neurology, or pulmology department. Second, arthritis was detected manually, and not by ultrasonography. Patients with myositis often have myalgia or hand edema and such symptoms can be mistaken as arthralgia or arthritis, which might have influenced the frequency of joint symptoms in this study. Third, antibody to anti-melanoma differentiation associated gene 5 (MDA5) was not examined. Patients with anti-MDA5 antibody have similar clinical manifestations to patients with ASA, such as ILD, Raynaud's phenomenon, fever, and arthritis[22, 32-34]. Patients positive for anti-MDA5 antibody have a high prevalence of arthritis (42－82%) and can present with polyarthritis[22, 32-34]. Thus, anti-MDA5 antibody may be positive in Japanese DM patients who have joint symptoms but are negative for anti-Jo-1 antibody.

In conclusion, anti-Jo-1 antibody was associated with joint symptoms in Japanese PM/DM patients. Anti-CCP antibody should be examined in patients with inflammatory myopathy who have joint symptoms. If it is positive, aggressive treatment with disease-modifying anti-rheumatic drugs may be considered to prevent future radiographic progression.

Declaration of interest：The authors have no conflict of interest to declare.

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日本人の多発性筋炎・皮膚筋炎患者にみられる関節症状

長嶋　孝夫，　室﨑　貴勝，本根　杏子，釜田　康行，永谷　勝也，岩本　雅弘，簑田　清次

自治医科大学内科学講座アレルギー膠原病学部門　住所　栃木県下野市薬師寺3311-1

要　　約

目的：日本人の多発性筋炎（PM）/皮膚筋炎（DM）患者にみられる関節症状に関連する臨床的特徴を検討する。
方法：2007年１月から2012年３月までに当科に入院した PM/DM 患者を対象とした。臨床徴候や検査値は診療録から後ろ向きに収集した。
結果：78人の患者（PM：20人，DM：58人）を対象とした。78人中，37人（47%）に関節炎・または関節痛がみられた。関節症状はPM患者よりもDM患者に多くみられたが，有意差はつかなかった（30% vs. 53%, P=0.07）。抗アミノアシルtRNA合成酵素抗体（抗ARS抗体）は25人（32%）に陽性となり，抗環状シトルリン化ペプチド抗体（抗CCP抗体）は７人（９%）が陽性だった。抗Jo-1抗体陽性患者は高頻度に関節炎を認め（82%），また抗Jo-1抗体陽性患者11人中４人（36%）が抗CCP抗体も陽性だった。関節症状があるPM/DM患者のうち，抗Jo-1抗体はPMの67%に陽性だが，DMでは16%しか陽性とならなかった。78人中４人は，PM/DMと診断されるまで関節リウマチとして治療されていた。多変量解析では発熱，Raynaud現象，抗Jo-1抗体が関節症状と関連がみられた。しかし，全ての抗ARS抗体でみると，関節症状の有無とは関連がみられなかった。
結論：PM/DM患者の47%に関節症状がみられた。抗Jo-1抗体を除いては，抗ARS抗体は日本人のPM/DM患者の関節症状と関連は認められなかった。
（キーワード：関節リウマチ，抗シンセターゼ抗体症候群，全身性強皮症，多発性筋炎，皮膚筋炎）

連絡先：長嶋孝夫，自治医科大学内科学講座アレルギー膠原病学部門，〒329-0498 栃木県下野市薬師寺3311-1，
E-mail：naga4ma@jichi.ac.jp
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