Chronological Evaluation of the Onset of Histologically Confirmed Interstitial Pneumonia Associated with Polymyositis/dermatomyositis

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Abstract

Objective The present study was designed to determine the chronological sequence of interstitial pneumonia, skin involvement, and muscle involvement associated with polymyositis/dermatomyositis (PM/DM).

Methods We examined our own cases of histologically confirmed interstitial pneumonia associated with PM/DM. In addition, a review of the literature was done to evaluate other cases of histologically confirmed interstitial pneumonia associated with PM/DM. Lung involvement was the first clinical symptom for all of our 8 patients.

Results Including the literature review and our 8 cases, there were 94 patients with PM/DM in whom interstitial pneumonia was histologically confirmed (36 PM, 50 DM, and 8 amyopathic DM). Chronological evaluation between the diagnosis of PM/DM and lung involvement demonstrated that most lung involvement occurred just before or just after the diagnosis of PM/DM. Interstitial pneumonia was preceded in 35 of 87 evaluable patients [21 cases with PM (61.8%), 14 cases with DM and amyopathic DM (40.2%)]. In 60 of 87 evaluable patients (69.0%), lung involvement occurred as a clinical manifestation at the diagnosis of PM/DM.

Conclusion The present data demonstrate that interstitial pneumonia was frequently the initial onset in patients with PM/DM.

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Key words: surgical lung biopsy, pathology, pulmonary fibrosis

Introduction

Interstitial lung involvement occurring in polymyositis/der-

matomyositis (PM/DM) was first described by Mills and Matthews in 1956 (1). Since then, various retrospective studies have described the relationship between PM/DM and diffuse interstitial lung disease (1–50). Tazelaar et al (22) reviewed specimens obtained at open lung biopsy from 14 patients with PM/DM and at autopsy from 1 patient, and reported 4 major groups based on the histologic patterns: bronchiolitis obliterans organizing pneumonia (BOOP), usual interstitial pneumonia (UIP), acute interstitial pneumonia (AIP), and cellular interstitial pneumonia (CIP). More recently, Katzenstein and Fiorelli (51) reported that 10 of their 64 patients with non-specific interstitial pneumonia (NSIP) had an association with connective tissue diseases, including two patients with PM. As it has been reported that interstitial lung disease affects the prognosis of PM/DM, and the prognosis of interstitial lung disease differs according to the histological findings (22), it is therefore important to evaluate the pathological types of interstitial lung disease. In addition, we believe that it is very important to evaluate the onset of lung involvement in relation to skin involvement and/or muscle involvement.

Considering this background, we evaluated the chronological sequence of the onset of interstitial pneumonia and compared that with the onset of skin lesions and/or muscle lesions.

Materials and Methods

Subjects

We first examined our own patients with a diagnosis of PM/DM (Table 1). PM/DM was diagnosed according to the criteria of Bohan and Peter (52) and Dalakas (53), and classified according to the criteria described by Tanimoto et al (54): (i) symmetric muscle weakness; (ii) typical histologic findings on muscle biopsy; (iii) increased levels of muscle enzymes in the sera; (iv) compatible electromyographic findings; and (v) characteristic dermatologic manifestations. The typical skin involvement of DM was confirmed when either Gottron's papules or heliotrope rash were identified. Other cutaneous lesions (e.g.,

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Table 1. Clinical Features of Patients with Interstitial Pneumonia Associated with Polymyositis/dermatomyositis

Case	Authors	References	Age & Sex	Clinical Diagnoses*	First Symptom ⁺	Intervals ⁺⁺ (Months)	Lung Specimens [§]	Outcome
1	Mills	1	52F	DM	L	-4	Autopsy	Dead
2	Goldfischer	2	62M	DM	S	3	SLB	Dead
3	Hyun	3	57F	DM	L	0	Autopsy	Dead
4	Sandbank	4	55F	DM	M	12	Autopsy	Dead
5	Weaver	5	40F	DM	L+S	0	SLB	Alive
6	Thompson	6	60F	PM	L	-3	SLB	Dead
7	Thompson	6	60M	PM	L+M	0	Autopsy	Dead
8	Olsen	7	48F	PM	L+M	0	SLB	Alive
9	〃	7	37F	PM	M	12	SLB	Alive
10	Webb	8	65M	PM	L	-1	SLB	Alive
11	Duncan	9	44F	DM	L+M+S	0	SLB	Alive
12	〃	9	39F	PM	L	-2	Autopsy	Dead
13	Krain	10	44M	DM	L+M+S	0	SLB	Alive
14	Schwarz	11	37M	DM	L	-3	SLB	Alive
15	〃	11	32F	PM	M	24	Autopsy	Dead
16	〃	11	61F	PM	L	-24	SLB	Alive
17	〃	11	51F	PM	L	-1	Autopsy	Dead
18	〃	11	60M	PM	L	-3	Autopsy	Dead
19	〃	11	64F	PM	M	5	SLB	Alive
20	Plowman	12	29M	DM	M+S	1	SLB	Alive
21	Fernandes	13	48M	Amyopathic DM	S	9	Autopsy	Dead
22	Hanawa	14	46F	PM	L	-12	SLB	Alive
23	Fergusson	15	58M	DM	S	1	Autopsy	Dead
24	〃	15	76F	DM	L+M+S	0	Autopsy	Dead
25	Schiavi	16	24F	DM	L	-4	SLB	Alive
26	Wasicek	17	59M	PM	L+M	0	SLB	Dead
27	Fudman	18	42F	Amyopathic DM	S	1	TBLB	Dead
28	〃	18	55F	Amyopathic DM	L+S	0	TBLB	Dead
29	Gruhn	19	34F	DM	L+M	0	TBLB	Alive
30	Takizawa	20	54F	DM	S	3	Autopsy	Dead
31	〃	20	50F	DM	L+M+S	0	TBLB	Dead
32	〃	20	53M	DM	L	-2	TBLB	Alive
33	Kobayashi	21	49F	DM	S	4	Autopsy	Dead
34	Tazelaar	22	47F	PM	L+M	0	SLB	Alive
35	〃	22	53F	PM	L+M	0	SLB	Alive
36	〃	22	19F	DM	L	-1	SLB	Dead
37	〃	22	31M	PM	L+M	0	SLB	Alive
38	〃	22	32F	DM	M+S	2	SLB	Dead
39	〃	22	73M	PM	L	-6	SLB	Alive
40	〃	22	57F	DM	M+S	36	SLB	Alive
41	〃	22	55F	DM	M+S	6	SLB	Dead
42	〃	22	72F	PM	L+M	0	SLB	Dead
43	〃	22	61M	DM	M+S	3	SLB	Dead
44	〃	22	40M	DM	S	0	SLB	Alive
45	〃	22	57M	DM	L+M+S	0	SLB	Dead
46	〃	22	67F	DM	L+M+S	0	SLB	Dead
47	〃	22	41M	DM	M+S	1	SLB	Dead
48	〃	22	58F	PM	L+M	0	SLB	Dead
49	Tokiyama	23	55F	Amyopathic DM	S	5	Autopsy	Dead
50	〃	23	46F	Amyopathic DM	S	11	Autopsy	Dead
51	Lambie	24	19M	PM	L	-1	TBLB	Alive
52	Mahler	25	65F	PM	L+M	0	TBLB	Alive
53	Imokawa	26	58F	PM	L	-4	SLB	Alive
54	Hsue	27	36F	PM	L	-10	SLB	Alive
55	Lohr	28	67	PM	L	-10	TBLB	Alive

Interstitial Pneumonia in PM/DM

56	Mouri	29	60F	DM	L	-2	SLB	Alive
57	Clawson	30	47F	PM	L+M	0	Autopsy	Dead
58	"	30	40F	PM	M	6	SLB	Dead
59	de Toro Santos	31	41F	DM	M+S	4	SLB	Dead
60	Ozawa	32	48F	DM	M+S	5	Autopsy	Dead
61	Nagai	33	69F	PM	L+M	0	TBLB	Alive
62	Grau	34	64M	DM	M+S	3	SLB	Alive
63	"	34	52F	DM	L+M+S	0	SLB	Alive
64	"	34	59F	DM	L+S	0	SLB	Alive
65	Ikuta	35	61F	PM	L	-1	SLB	Alive
66	Fata	36	51M	PM	L	-2	SLB	Alive
67	Kalenian	37	53M	DM	L+M	0	SLB	Alive
68	Shinohara	38	56F	DM	L	0	SLB	Alive
69	Asanuma	39	48F	Amyopathic DM	S	12	SLB	Alive
70	Kiely	40	66M	PM	L	-6	SLB	Alive
71	Nobutoh	41	47F	DM	L	-3	Autopsy	Dead
72	Satoh	42	62M	PM	L	-3	TBLB	Alive
73	Satomi	43	59F	DM	M+S	3	TBLB	Alive
74	Takahashi	44	56M	PM	L	-3	TBLB	Alive
75	Ito	45	41M	DM	Unclear	1	Autopsy	Dead
76	"	45	49F	DM	Unclear	3	Autopsy	Dead
77	"	45	43M	DM	Unclear	1	Autopsy	Dead
78	"	45	61F	DM	Unclear	2	Autopsy	Dead
79	"	45	58F	DM	Unclear	1	Autopsy	Dead
80	"	45	26F	DM	Unclear	4	Autopsy	Dead
81	"	45	34M	DM	Unclear	0	Autopsy	Dead
82	Itoh	46	44F	DM	S	2	TBLB	Alive
83	Knoell	47	44F	DM	L	-2	SLB	Alive
84	Takashi	48	42M	Amyopathic DM	L+S	0	SLB	Alive
85	Lee	49	46F	DM	S	3	SLB	Alive
86	Nanke	50	53M	Amyopathic DM	L+S	0	Autopsy	Dead
87	Present study	-	58M	DM	L	-24	SLB	Dead
88	"	-	70F	DM	L	-2	SLB	Dead
89	"	-	65F	PM	L	-7	SLB	Alive
90	"	-	56F	DM	L	-3	SLB	Alive
91	"	-	60F	PM	L	-3	SLB	Alive
92	"	-	57M	PM	L	-1	SLB	Alive
93	"	-	45F	DM	L	-6	SLB	Alive
94	"	-	63F	PM	L	-12	SLB	Alive

*PM: polymyositis, DM: dermatomyositis, *L: lung (interstitial pneumonia), M: muscle involvement, S: skin lesions. **Interval: months from the diagnosis of polymyositis/dermatomyositis to the onset of interstitial pneumonia. §SLB: surgical lung biopsy, TBLB: transbronchial lung biopsy.

mechanical hands, cuticular hyperplasia, or sun related erythema) were also considered to be skin involvement of DM (52).

The median age of our 8 patients with PM/DM was 59.3 years old with a range of 45 to 70 years (2 males and 6 females). The diagnoses of interstitial pneumonia were made on clinical, radiological, physiological, and histological grounds. The criteria used included: history of exertional dyspnea and cough, fine crackles on physical examination, compatible findings on the chest radiograph, physiologic abnormalities of restrictive lung defects including decreased diffusing capacity, and abnormal PaO₂ at rest and/or with exertion. In all patients, high resolution computed radiographic scanning of the lungs was performed. Histological confirmation was obtained by open lung biopsy (6 cases) or autopsy (2 cases). No patients received

immunosuppressive treatment such as corticosteroid or cyclophosphamide at the time of open lung biopsy. The histology of 6 patients with interstitial pneumonia associated with PM/DM had the pattern of NSIP according to the criteria described by Katzenstein and Fiorelli (51). Two patients fulfilled the clinical and pathologic criteria of AIP as described by Katzenstein et al (55).

Literature Review

In addition to our 8 cases with histologically confirmed interstitial pneumonia, we reviewed case reports concerning PM/DM associated with interstitial pneumonia through MEDLINE. Articles not listed in MEDLINE and those written in languages other than English or Japanese were excluded.

There are seven subsets of myositis (53, 54): DM, PM, myo-

sitis with cancer, childhood PM and DM, myositis overlapping with another collagen-vascular disorder, amyopathic DM (56), and inclusion-body myositis (57). Among them, cases with myositis with cancer, childhood PM (age less than 16), myositis overlapping with another collagen-vascular disorder, or inclusion-body myositis were excluded.

Since pulmonary complications associated with PM/DM were heterogeneous (for example aspiration pneumonia or opportunistic infections), patients without histological confirmation of interstitial pneumonia were also excluded. In addition, patients whose clinical description was inadequate for evaluating the chronological sequence of the onset of interstitial pneumonia were also excluded.

Finally, including the present 8 cases, 94 cases (1–50) were reviewed (Table 1) to evaluate the chronological sequence of interstitial pneumonia. The diagnosis of interstitial pneumonia was made by surgical lung biopsy in 55 cases, autopsy in 26 cases, and transbronchial lung biopsy in 13 cases.

Criteria for the Onset of Interstitial Pneumonia, Skin Lesions, and Muscle Involvement

Since all cases were histologically confirmed to be interstitial pneumonia, it is reasonable to assume that the respiratory symptoms were caused by interstitial pneumonia. However, to be more precise, the following criteria were used. As for clinical symptoms, cough as well as dyspnea were considered to represent the onset of interstitial pneumonia. Cough, sputum, or chest pain, as a single symptom was not considered to indicate the onset of interstitial pneumonia. Chest X-ray or chest CT abnormality compatible with interstitial pneumonia was considered to indicate the onset of interstitial pneumonia.

Skin rashes typical or compatible with DM as described previously were considered as the onset of skin lesions in patients with DM or amyopathic DM. Progressive, proximal, generalized weakness and/or myalgia were considered as the onset of myositis in patients with PM/DM. An increased concentration of muscle enzymes and/or abnormalities in electromyogram was also considered to indicate the existence of myositis in PM/DM and amyopathic DM.

Results

In all of the present 8 patients, lung involvement was the first clinical symptom of onset (Fig. 1). With the literature review and our 8 cases, there were 94 patients with PM/DM in whom interstitial pneumonia was histologically confirmed (36 PM, 50 DM, and 8 amyopathic DM) (Table 2). There were 62 females, 31 males, and 1 non-described.

In total, anti-Jo-1 antibody was positive in 17 of 40 (42.5%) described cases (among the 94 cases, the results of anti-Jo-1 antibody were not described in 54 cases). In the present cases, rheumatoid factor was detected in case #88 and case #91 (case numbers are as listed in Table 1). Anti-nuclear antibody was detected in case 91, case 92, and case 93. Anti-Jo-1 antibody was detected in case 90 and case 94.

Methods of lung biopsy, pathological classifications, and

Figure 1. Chronological evaluation of the onset of interstitial pneumonia, skin lesions, and/or the muscle involvement in the present 8 patients with polymyositis/dermatomyositis (PM/DM). L: lung lesions, S: skin lesions, M: muscle involvement. Arrow: onset of lung lesions in our 8 cases. Triangle: at the time of clinical diagnosis of PM/DM. Numbers of vertical axis: months from the diagnosis of PM/DM (triangle) to the onset of interstitial pneumonia (arrow). In all 8 patients with polymyositis/dermatomyositis, interstitial pneumonia was observed as the initial onset of clinical symptoms of PM/DM.

outcome are also listed in Table 2. Since definite pathological classification had not been established previously, we simply classified those cases (pathological classification could not be evaluated) as pulmonary (interstitial) fibrosis. About one-half of the patients died of respiratory failure due to interstitial pneumonia.

The chronological evaluation between the onset of interstitial pneumonia and the onset of skin lesions or muscle lesions are listed in Table 2 and also shown in Fig. 2. Chronological evaluation between the onset of PM/DM and lung involvement demonstrated that most lung involvement occurred just before or just after the onset of PM/DM (Fig. 2). Interstitial pneumonia was preceded in 35 of 87 patients (21 cases with PM and 14 cases with DM [40.2%, Table 3]). In 60 of 87 patients (69.0%, including the 35 preceding cases), lung involvement was observed at the onset of PM/DM. In addition, skin involvement was observed at the onset of DM and amyopathic DM in 34 patients (39.1%) and muscle involvement was observed at the onset of PM/DM in 35 patients (40.2%), respectively.

Although interstitial pneumonia tended to be the initial onset more frequently in cases diagnosed by chest CT compared with cases diagnosed by chest X-ray only, there were no significant statistical differences between the 2 groups ($p=0.1096$, χ^2 -square test).

Discussion

PM/DM are multisystem disorders of unknown cause which occur in all age groups, but predominate in mid-adult life and

Table 2. Patient Characteristics (Total 94 Patients)

	Age (Median [range])	Case number (Female/Male/Undescribed)
PM	58 [19–73]	36 (23/12/1)
DM	51 [19–76]	50 (34/16/0)
Amyopathic DM	48 [46–55]	8 (5/3/0)
Methods of histological evaluation		
Surgical lung biopsy		55
TBLB*		13
Autopsy		26
Pathological classification ⁺		
Pulmonary (interstitial) fibrosis		32
BOOP		18
DAD		18
NSIP		8
UIP		5
DIP		1
Undetermined (TBLB cases)		12
Outcome		
Alive		49
Dead		45

*TBLB: transbronchial lung biopsy, *BOOP: bronchiolitis obliterans organizing pneumonia, DAD: diffuse alveolar damage, NSIP: non-specific interstitial pneumonia, UIP: usual interstitial pneumonia, DIP: desquamative interstitial pneumonia.

Figure 2. The chronological comparison between the onset of interstitial pneumonia and the onset of skin lesions or muscle lesions in 94 patients with polymyositis/dermatomyositis. Numbers of horizontal axis: months from the diagnosis of polymyositis/dermatomyositis to the onset of interstitial pneumonia. Most interstitial pneumonia occurred just before or just after the onset of PM/DM. In 34 cases, interstitial pneumonia preceded skin lesions and/or muscle involvement.

are more common in women. Although the skin and muscles are the most commonly affected organs, pulmonary disease occurs in as high as 45% of PM/DM patients (58).

In PM/DM, the lung may be involved either primarily as in interstitial lung diseases and rarely in primary pulmonary hypertension, or it may be involved secondarily as a complication of striated muscle dysfunction leading to aspiration or to ventilatory insufficiency (58). In addition, lung disease may also occur as a *sequela* of the treatment of PM/DM such as in drug-induced interstitial pneumonitis and opportunistic lung infection (58).

In the present study, we demonstrated that interstitial pneumonia frequently occurred at the onset of PM/DM. Although the pathogenesis of pulmonary complications observed in PM/DM are heterogeneous as listed above, we only evaluated cases in which the existence of interstitial pneumonia was histologically confirmed. Therefore, patients evaluated in the present study were believed to have definite interstitial pneumonia associated with PM/DM. However, since we only evaluated the histologically confirmed cases and because it is generally difficult to perform surgical lung biopsy in acute progressive cases or severely affected cases, it is possible that relatively chronic and mild cases were included in the study.

In the present study, in addition to our own 8 cases, we list patients from the reported literature. Therefore, bias of reviewing case reports should be discussed. In our 8 cases, there was no selection of patients. In addition, in the report of Schwarz et al (11) (6 cases) as well as in the report of Tazelaar et al (22)

(15 cases), it was believed that there was no patient selection. In these reports, as observed in all of our 8 cases, interstitial pneumonia occurred before the onset of PM/DM in 4 of 6 cases reported by Schwarz et al (11) and in 2 of 15 cases reported by Tazelaar et al (22). In contrast, in the report of Ito et al, they selected 7 retrospective cases with DM accompanied by rapidly progressive interstitial lung disease (45), diffuse alveolar damage was diagnosed in all cases by autopsy. Therefore, this report had a significant bias. In addition, there might be a bias in that an aggressive form of interstitial pneumonia and patients with amyopathic DM (frequently complicated with AIP) were collected. However, even if we selectively evaluated patients with PM, the tendency for lung onset was higher compared with DM as well as amyopathic DM.

Since lung involvement was observed at the diagnosis of PM/DM in all of the present 8 cases (including 7 preceding cases), it was suggested that the diagnosis of interstitial pneumonia had been very early in our cases compared with previously reported cases. This evidence might be a result of the early chest CT examination for the diagnosis of interstitial pneumonia in our department.

We also demonstrated that in patients with DM and amyopathic DM, skin lesions frequently occurred before the onset of interstitial pneumonia. This finding was reasonably understood because skin lesions were easily recognized by patients. In contrast, in patients with PM, lung involvement frequently occurred before the onset of muscle symptoms. It is obvious that the diagnosis of PM is uncommonly made in the early stages, the reason being i) general unfamiliarity with the condition, ii) variability in the mode of onset, iii) insidious onset of weakness simulating muscular dystrophy in many cases, and iv) the initial symptom is nonmuscular in more than one-third of the cases (59).

Since a wide range of clinical presentations is manifested by interstitial pneumonia, it should also be considered that interstitial pneumonitis was not diagnosed at the onset of PM/DM. It is obvious that interstitial pneumonia is diagnosed with more sensitivity using a chest CT than a chest X-ray. In addition, since our cases were histologically confirmed as interstitial pneumonia, it is possible to perform histological classification, for example, UIP, NSIP, BOOP, or AIP. Among these types, UIP revealed chronic pathological changes, and therefore, cases diagnosed histologically to be UIP should be carefully evaluated. In the present study, in some cases (cases 4, 9, 15, 40, and 69), UIP was histologically diagnosed after the onset of skin and/or muscle involvement. Cases 4 (4), 9 (7), and 69 (39) were diagnosed after 12 months, case 15 (11) was diagnosed after 24 months, and case 40 (22) was diagnosed after 36 months from the onset of PM/DM. Since UIP is believed to be the pathological finding of chronic interstitial pneumonia, it was speculated that interstitial pneumonia was diagnosed very late in these cases.

The etiology and pathogenesis of interstitial pneumonia associated with PM/DM remains obscure. It is believed that the initial lung injury is immunologically mediated because of the prominent infiltration of immune effector cells observed in early

lesions. The relative importance of cell-mediated immunity, cytotoxic antibodies, and immune complex injury remains unclear. Experimental evidence supports a more important role for cell-mediated than for humoral immunity in the pathogenesis of the myositis of PM/DM (58). Fata et al (36) reported that the relationship between BOOP and PM suggests that a common exogenous antigen or autoantigen may become the target of a cell-mediated immune response in the lung and the muscle. Since clinical evidence of interstitial pneumonia often precedes the clinical presentation of muscle disease, it might be important to search for specific respiratory pathogens (virus, and/or bacteria) in the pathogenesis of PM/DM associated with interstitial pneumonia.

In conclusion, our data demonstrate that pulmonary manifestation was frequently the first onset of PM/DM complicated with interstitial pneumonia.

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