

Myalgia in Patients with Dermatomyositis and Polymyositis Is Attributable to Fasciitis Rather Than Myositis: A Retrospective Study of 32 Patients who Underwent Histopathological Examinations

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ABSTRACT. Objective. To determine the association between fasciitis and the clinical variables in patients with dermatomyositis (DM) and polymyositis (PM).

Methods. We retrospectively reviewed the medical records of 32 patients (24 DM, 8 PM) with newly diagnosed DM and PM and in whom fascia and muscle specimens were histopathologically examined. The relationship between fasciitis and the clinical variables was statistically analyzed. These included age, sex, myalgia, muscle weakness, creatine kinase (CK) and aldolase activities, anti-Jo1 antibody, interstitial lung disease, and malignancy.

Results. Twenty (62.5%) of the 32 patients who underwent the histopathological examination of a fascia specimen had fasciitis, including 18 (75%) of 24 patients with DM and 2 (25%) of 8 patients with PM. The frequency of fasciitis was significantly higher among the patients with DM than among the patients with PM ($p < 0.05$). Histopathologically, fasciitis in PM was very mild in comparison to that in DM. The frequency of myalgia in patients with fasciitis was significantly higher than that in patients without fasciitis ($p < 0.05$). However, myalgia was not associated with myositis. There were no significant differences in the patients with and without fasciitis in age, sex, manual muscle test 8 scores, CK or aldolase activities, or the presence of anti-Jo1 antibodies and malignancy.

Conclusion. The frequency of fasciitis was significantly higher among patients with DM than among those with PM. Fasciitis, rather than myositis, was associated with myalgia. (First Release February 1 2017; J Rheumatol 2017;44:482–7; doi:10.3899/jrheum.160763)

Key Indexing Terms:

DERMATOMYOSITIS POLYMYOSITIS FASCIITIS MYOSITIS MYALGIA

Dermatomyositis (DM) and polymyositis (PM) are classified as inflammatory myopathies caused by an autoimmune mechanism. Muscle weakness and myalgia are the major symptoms associated with inflammatory myopathies. The main classification criterion for DM or PM (in the Bohan and Peters criteria) is muscle weakness¹. However, Tanimoto's criteria, which are used primarily in Japan, include not only muscle weakness but also myalgia². Tomimitsu, *et al* reported that, in a Japanese survey, the frequencies of "muscle pain or tenderness" and "proximal muscle weakness" in the upper or

lower extremities were 73.7% and 87.7%, respectively, among newly registered patients with DM or PM in 2009³. Therefore, these muscle symptoms were deemed important for diagnosing DM or PM. Muscle weakness is attributed to a decrease in the muscle fibers due to the inflammation of muscles. The cause of myalgia has been described as nociceptive stimulation in the fascia attributable to neutrophilic factors derived from muscle fibers or inflammatory cells^{4,5,6}. We previously reported that inflammation in the fascia of patients with DM occurred early⁷. The development of fasciitis in DM may be an important finding for understanding the pathology of myositis. However, it remains unknown whether it is associated with clinical symptoms or various complications. In patients with suspected myositis who present with muscle symptoms, such as pain and weakness, biopsy specimens from the affected muscle often fail to show inflammatory cell infiltration in the muscle fibers^{8,9,10}. To date, the muscle symptoms of myositis are believed to occur primarily because of myositis rather than fasciitis. Thus, in the current study, we retrospectively reviewed the medical records of patients with newly diagnosed DM and PM whose fascia and muscle tissue were

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histopathologically examined. The relationship between fasciitis and the clinical variables was analyzed.

MATERIALS AND METHODS

Patients. In the current study, we retrospectively reviewed the medical records of newly diagnosed patients with DM and PM according to the criteria of Bohan and Peter¹. The patients were admitted to the Division of Rheumatology at Jikei University Hospital between April 2007 and December 2013. The study population of 54 Japanese patients included 35 with DM [including 9 with clinically amyopathic dermatomyositis (CADM)] and 19 with PM. Thirty-two of the 54 patients underwent *en bloc* biopsy or myofascial biopsy; the biopsy specimens were histopathologically examined to detect fasciitis and myositis. We also collected clinical information about DM and PM from the medical records and analyzed the relationship between fasciitis and the clinical variables. The clinical variables included the patients' age, sex, clinical symptoms (myalgia and muscle weakness), the serum activities of creatine kinase (CK) and aldolase, and the presence of anti-Jo1 antibody, interstitial lung disease (ILD), and malignancies. Myalgia was defined as tenderness of the muscle and/or spontaneous muscle pain. Muscle weakness was evaluated using a manual muscle test (MMT). The strength of the spinal muscles (neck flexors), proximal muscles (deltoid, biceps brachii, gluteus maximus, gluteus medius, and quadriceps femoris muscles), and the distal muscles (forearm and ankle flexors) on 1 side was graded as 0, 2-, 2+, 3-, 3+, 4-, 4+, and 5 on a 0–10 scale; and the total points for the respective muscles were regarded as the MMT8 score¹¹. DM and PM were classified as "definite" or "probable" according to the criteria of Bohan and Peter¹. DM consistent with amyopathic or hypomyopathic dermatomyositis was classified as CADM¹². This study was approved by the Ethics Committee of Jikei University School of Medicine (approval number 26-267[7773]).

Histopathology. Muscle magnetic resonance imaging (MRI) was performed to investigate the sites of muscle weakness or pain. In patients without muscle weakness or pain, MRI of the brachial and femoral regions was performed. *En bloc* biopsy was performed in patients whose MRI findings suggested muscular or fascial involvement and who provided us with their informed consent. Patients whose subcutaneous fat was too thick to perform *en bloc* biopsy underwent myofascial biopsy. If the myofascial MRI findings were negative, *en bloc* biopsy was performed at the sites of muscle weakness or pain. *En bloc* biopsy was done as previously reported⁷. All of the biopsy samples were fixed in 10% neutral-buffered formalin and embedded in paraffin. The block was sectioned into 3- μ m slices. The sections were prepared for histopathological examination with H&E. A pathologist and rheumatologist assessed all of the specimens to identify histopathological changes. Inflammatory cell infiltration around the muscle fibers or intramuscular small blood vessels was interpreted as indicating the presence of myositis. Inflammatory cell infiltration in the fascia (including the epifascial and subfascial tissues) was regarded as indicating the presence of fasciitis. Fasciitis was evaluated using a modified version of our previously described method⁷. Briefly, microscopic fields showing clear signs of inflammation were identified in the tissue sections. In addition, the 4-mm² area with the most severe inflammatory cell infiltration in each microscopic field was identified. The number of areas with microvessels surrounded by inflammatory infiltration consisting of more than 50 cells was counted; this number was recorded as the vascular inflammation score (VIS)¹³. The sum of the VIS in 3 microscopic fields was defined as the total vascular inflammation score (TVIS). TVIS of 0, 1–2, and ≥ 3 were used to define the absence of fasciitis, mild fasciitis, and significant fasciitis, respectively. Fasciitis included mild and significant fasciitis.

Statistical analysis. The Mann-Whitney U test was used to analyze differences in the age, MMT8 scores, CK, and aldolase activities of the patients with DM and PM. Fisher's exact test was used to analyze the differences in the frequency of fasciitis and myositis in the histopathological examinations, and sex, myalgia, the presence of anti-Jo1 antibody, ILD, and malignancy. The Mann-Whitney U test was used to examine the differences in the age,

MMT8 scores, CK activities, and aldolase activities due to the presence or absence of fasciitis and myositis on histopathological examinations. Fisher's exact test was used to analyze the differences in the patients' sex, the frequency of myalgia, and the presence of anti-Jo1 antibody, ILD, and malignancy. All of the statistical analyses were performed using the GraphPad Prism (version 4.0). P values < 0.05 were considered to indicate statistical significance.

RESULTS

Patient profiles. The fascia and muscle tissue specimens were histopathologically examined in 32 patients, consisting of 24 with DM (including 6 with CADM) and 8 with PM (Table 1). None of the patients with PM showed finger flexor weakness, which is included in the diagnostic criteria for inclusion body myositis proposed by Lloyd, *et al*¹⁴. Further, all patients with PM responded to treatment with prednisolone either alone or in combination with immunosuppressive agents. There were no differences in age or sex between DM and PM. Seventeen (70.83%) of the 24 patients with DM and 2 (25%) of the 8 patients with PM had myalgia. The frequency of myalgia in DM was significantly higher than in PM ($p < 0.05$). The mean MMT8 scores of the DM and PM patients were 76.38 ± 3.321 and 79.5 ± 0.9258 , respectively; indicating that the mean MMT8 score of the patients with DM was significantly lower than that of the patients with PM ($p < 0.05$). The mean serum CK and aldolase activities in the DM and PM patients did not differ to a statistically significant extent. There was no difference in the frequency of anti-Jo1 antibody positivity or in the rate of malignancy between DM and PM. The frequency of ILD in patients with DM was significantly higher than that in patients with PM ($p < 0.05$). The fascia tissue specimens were not histopathologically examined in 22 patients who were not biopsied, including 11 patients with DM (3 with CADM) and 11 patients with PM (Supplementary Table 1, available with the online version of this article). There were no marked differences in the profiles of the patients with DM and those with PM between the biopsied and non-biopsied groups.

Histopathological findings. A histopathological examination was performed for 32 of the 54 patients [*en bloc* biopsy ($n = 27$); myofascial biopsy ($n = 5$)]. Figure 1 shows the gadolinium contrast-enhanced, fat-suppressed, T1-weighted MRI findings in the patients as analyzed in this study. The MRI finding of fascial involvement in patients with DM varied from the involvement of only the partial fascia of 1 muscle to that of more than 1 muscle (Figure 1A). The degree of fascial involvement, if any, was markedly less in patients with PM than in patients with DM (Figure 1B). Fascial involvement on MRI was observed in 36 (66.67%) of the patients: in 29 (82.86%) of 35 with DM and 7 (36.84%) of 19 with PM (Supplementary Table 2). There were no marked differences in the frequencies of fascial or muscular involvement between the biopsied and non-biopsied groups among the patients with DM and the patients with PM. Fasciitis was histopathologically detected in 20 (62.53%) of

Table 1. The characteristics of the DM and PM patients who underwent a biopsy of the fasciae and muscles. The values indicate the number of patients (%) or the mean \pm SD.

Variables	DM, n = 24	PM, n = 8	Total, n = 32	p
Age, yrs	53 \pm 12.33	58.88 \pm 10.47	54.47 \pm 12.01	NS*
Sex, M/F	10/14	2/6	12/20	NS**
Myalgia	17 (70.83)	2 (25)	19 (59.38)	< 0.05**
MMT8	76.38 \pm 3.321	79.5 \pm 0.9258	77.16 \pm 3.204	< 0.05*
CK, IU/l ^a	1491 \pm 2416	1961 \pm 1699	1608 \pm 2242	NS*
Aldolase (IU/l) ^b	23.46 \pm 33.01	28.86 \pm 27.60	24.06 \pm 31.44	NS*
Anti-Jo1	4 (16.67)	1 (12.5)	5 (15.63)	NS**
ILD	20 (83.33)	3 (37.5)	23 (71.88)	< 0.05**
Malignancy	4 (16.67)	2 (25)	6 (18.75)	NS**

^a Normal range, 25–200 IU/l. ^b Normal range, 2.1–6.1 IU/l. * Mann-Whitney U test; ** Fisher's exact test. DM: dermatomyositis; PM: polymyositis; CK: creatine kinase; MMT: manual muscle testing; anti-Jo1: anti-Jo1 antibody; ILD: interstitial lung disease; NS not significant.

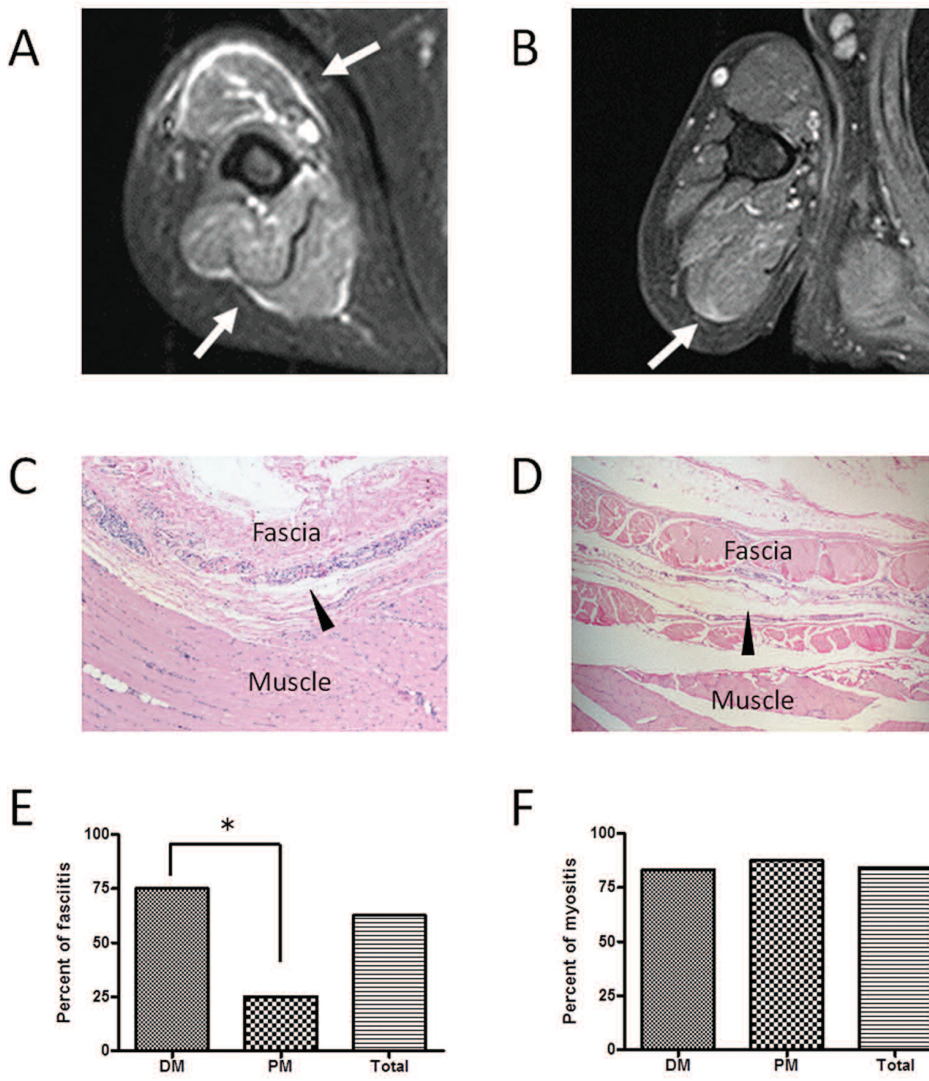


Figure 1. The gadolinium-enhanced fat-suppressed T1-wedged magnetic resonance imaging (MRI) and histopathological findings from patients with newly diagnosed dermatomyositis (DM) and polymyositis (PM). A. MRI of the upper arm in a DM case shows areas of high signal intensity in the muscle and fascia of the biceps brachii and triceps brachii. B. MRI of the upper arm in a PM case shows areas of high signal intensity in the muscle and fascia of the triceps brachii. The pathological findings from the examination of *en bloc* biopsy specimens from patients with newly diagnosed DM and PM with H&E staining. C. H&E-stained biceps brachii muscle tissue from the same DM case as in panel A reveals mononuclear cell infiltration around the subfascial capillaries, venules, and in the endomysia. D. H&E-stained triceps brachii muscle tissue from the same PM case as panel B shows weak mononuclear cell infiltration in the fascia (original magnification \times 100 in panels C and D). E. Fasciitis was histopathologically detected in 20 (62.5%) out of 32 patients; specifically, in 18 (75%) out of 24 patients with DM and 2 (25%) out of 8 with PM. F. Myositis was detected in 27 (84.38%) out of 32 patients; specifically, in 20 (83.33%) out of 24 patients with DM and 7 (87.5%) out of 8 with PM. The frequency of fasciitis was significantly higher among the patients with DM. * $p < 0.05$.

Table 2. Associations between the pathological findings and clinical variables. The values indicate the number of patients (%) or the mean \pm SD.

Variables	Fasciitis		p	Myositis		p
	Positive, n = 20	Negative, n = 12		Positive, n = 27	Negative, n = 5	
Age, yrs	53.6 \pm 12.54	55.92 \pm 11.45	NS*	54.11 \pm 12.39	56.41 \pm 10.64	NS*
Sex, M/F	9/11	3/9	NS**	9/18	3/2	NS**
Myalgia	15 (75)	4 (33.33)	< 0.05**	17 (62.96)	2 (40)	NS**
MMT8	76.95 \pm 3.395	77.5 \pm 2.970	NS*	77.15 \pm 3.243	77.2 \pm 3.347	NS**
CK, IU/l ^a	2116 \pm 2678	1212 \pm 1224	NS*	1664 \pm 2358	1307 \pm 1628	NS*
Aldolase, IU/l ^b	27.75 \pm 36.67	18.08 \pm 19.93	NS*	24.41 \pm 31.98	22.16 \pm 31.77	NS*
Anti-Jo1	5 (25)	0	NS**	5 (18.52)	0	NS**
ILD	16 (80)	7 (58.33)	NS**	19 (70.37)	4 (80)	NS**
Malignancy	4 (20)	2 (16.67)	NS**	5 (18.52)	1 (20)	NS**

^a Normal range, 25–200 IU/l. ^b Normal range, 2.1–6.1 IU/l. * Mann-Whitney U test. ** Fisher's exact test. CK: creatine kinase; anti-Jo1: anti-Jo1 antibody; MMT: manual muscle testing; ILD: interstitial lung disease; NS: not significant.

the 32 patients; specifically, in 18 (75%) of 24 with DM and 2 (25%) of 8 with PM (Figure 1E). The frequency of fasciitis in patients with DM was significantly higher than that in patients with PM ($p < 0.05$). Myositis was observed in 27 (84.38%) of the 32 patients; specifically, in 20 (83.33%) of the 24 with DM and 7 (87.50%) of the 8 with PM (Figure 1F). There was no difference between the DM and PM patients in the frequency of myositis. The severity of fasciitis was evaluated using the TVIS. The TVIS was ≥ 3 in 13 patients, and 1–2 in 2 of the 18 patients with DM (Figure 1C). Two patients with PM had mild fasciitis, defined as a TVIS of 1 or 2, but did not have significant fasciitis, as defined by a TVIS of ≥ 3 (Figure 1D).

Clinicopathological analysis. We analyzed the relationship between the histopathological findings and the clinical variables associated with DM and PM (Table 2). These were age, sex, myalgia, MMT8 score, muscle enzyme activities (the CK and aldolase activities), the presence of anti Jo1 antibody, ILD, and malignancy. There was no difference in the age or sex of the patients with and without fasciitis or myositis. Fifteen out of 20 patients (75%) with fasciitis had myalgia, whereas 4 out of 12 patients (33.33%) without fasciitis had myalgia. The frequency of myalgia among patients with fasciitis was significantly higher than that among patients without fasciitis ($p < 0.05$). Seventeen out of the 27 patients (62.96%) with myositis had myalgia, whereas 2 out of 5 patients (40%) without myositis had myalgia. The frequency of myalgia between the patients with and without myositis did not differ to a statistically significant extent. The mean MMT8 scores, serum CK, and aldolase activities in the patients with and without fasciitis or myositis did not differ to a statistically significant extent. There was no difference between the patients with and without fasciitis or myositis in the frequency of anti-Jo1 antibody positivity, ILD, or malignancy.

DISCUSSION

We found that among the clinical variables, only myalgia (and not myositis) was associated with fasciitis. To our

knowledge, no reports have been published on the association between myalgia and fasciitis in DM and PM. Free nerve endings are abundantly distributed in the fasciae, and fasciitis easily causes myalgia because the inflammation may stimulate these nerve endings^{15,16}. The frequency of myalgia in patients with DM was higher than in patients with PM. This suggests that differences in the frequency of myalgia between DM and PM may be attributable to fasciitis. Indeed, while there were no marked differences in the activities of CK and aldolase between the patients with DM and those with PM, the mean MMT8 score of the patients with DM was significantly lower than that of the patients with PM. Myalgia may therefore affect the assessment of muscle strength in patients with DM.

Allen, *et al* in 2003 initially described a patient with CADM who had fasciitis¹⁷. With the exception of our past report, only 6 patients with fasciitis associated with inflammatory myopathy [2 with CADM, 2 with DM, and 2 with aminoacyl-tRNA synthetase (ARS) syndrome] have been described, to our knowledge (Table 3)^{17,18,19,20,21}. There are few past reports on fasciitis associated with myositis; however, our results suggest that fasciitis associated with myositis is more common. The severity and the frequency of fasciitis in patients with DM were significantly greater than in patients with PM. The results suggest that the fascia may be a target of inflammation in patients with DM; however, it remains unclear why this is the case. In DM, injury occurs in the border between adjacent tissues, such as perifascicular atrophy in the muscles or a lichenoid tissue reaction in the skin²². The fascia is also located in the border region between the subcutaneous connective tissue and muscle, thus raising the suspicion that injury may occur owing to a border effect²³.

Two of the 8 patients with PM who had fasciitis were positive for anti-ARS antibodies (anti-Jo1 and anti-PL7 antibodies; data not shown). Ebbo, *et al* reported 2 cases in which anti-Jo1-positive ARS syndrome was complicated with fasciitis in patients without skin manifestations¹⁸.

Table 3. Previous reports of cases in which fasciitis was complicated with inflammatory myopathy.

Case	Year	Author	Age/Sex	Disease	CK, U/ml	MRI	Pathology	Myalgia	Jo1
1	2003	Allen, <i>et al</i> ¹⁷	39/F	CADM	Normal	+	+	-	-
2	2004	Tsuruta, <i>et al</i> ²¹	50/F	CADM	Normal	+	+	+	-
3	2005	Lazaro, <i>et al</i> ¹⁹	29/F	DM	Normal	ND	+	+	-
4	2012	Riolo and Towheed ²⁰	36/M	DM	183	+	ND	+	-
5	2013	Ebbo, <i>et al</i> ¹⁸	33/M	ARS	9415	+	+	+	+
6	2013	Ebbo, <i>et al</i> ¹⁸	43/F	ARS	1800	+	+	+	+

DM: dermatomyositis; CADM: clinically amyopathic dermatomyositis; ARS: aminoacyl-tRNA synthetase antibodies syndrome; CK: creatine kinase; MRI: magnetic resonance imaging; ND: not described.

Among the patients in our analysis, all of those positive for the anti-Jo1 antibody had fasciitis. Each anti-ARS antibody, including the anti-Jo1 antibody, may be one of the factors associated with fasciitis in DM and PM. Therefore, fasciitis may occur in patients with PM who have anti-ARS antibodies. The differences in the clinical features of DM and PM have been analyzed according to the type of myositis-specific antibodies (MSA), including ARS antibodies, anti-melanoma differentiation-associated protein 5 antibodies, and others^{24,25}. In our current study, we did not fully examine the patients for the presence of anti-ARS antibodies or other MSA (with the exception of anti-Jo1 antibodies). Further studies are required to confirm the association between MSA positivity and fasciitis.

The fascia is a new target organ in DM and PM. Our data suggest that the frequency of fasciitis in patients with DM was significantly higher than that in patients with PM and that fasciitis was associated with myalgia. This finding is important when considering the clinical features in DM and PM. For instance, in patients with suspected DM or PM who present with myalgia but without muscle weakness, if fasciitis is histopathologically detected instead of myositis, the fasciitis is likely to contribute to myalgia and should be treated. Analyzing the cause of inflammation in the fasciae is likely to help uncover a pathogenesis for DM and PM.

Our study has several limitations. First, in 22 of the 54 patients, fascia specimens were not examined. We analyzed the patient profiles and the frequency of fascial involvement on MRI between the biopsied and non-biopsied groups among the DM and PM patients and found no statistical differences between the groups. However, we were unable to completely exclude the possibility of sampling bias. Second, there might be a false-negative histopathological finding due to a sampling error. Fasciitis and myositis were evaluated by a myofascial biopsy combined with MRI to make an accurate diagnosis. Van De Vlekkert, *et al* reported that muscle biopsy after MRI had the false-negative rate of 0.19⁹. We should pay attention to this possibility. Third, biopsy specimens are only a part of the whole lesion in the patient. The lesion may develop with a scattered distribution of inflammation. Thus, the histopathological findings may not always reflect the clinical variables. Fourth, the number of patients with PM

was too small to accurately evaluate the frequency of fasciitis in PM. A further investigation to address this issue is warranted.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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