Clinical, serologic and magnetic resonance imaging (MRI) study of 3 cases of inflammatory myopathy with abundant macrophages (IMAM) from Japanese population

Shintaro Hara, MD[a], Tomoko Henmi, MD[b], Atsushi Kawakami, MD, PhD[b], Keita Fujikawa, MD, PhD[b], Hiroshi Mukae, MD, PhD[c*], Noriho Sakamoto, MD, PhD[a], Kenzou Kaji, MD, PhD[d], Manabu Fujimoto MD, PhD[d], Masataka Kuwana MD, PhD[e], Toshiaki Tsukada, MD, PhD[f], Katsuya Satoh, MD, PhD[b], Masakatsu Motomura, MD, PhD[b], Mami Tamai, MD, PhD[b], Hideki Nakamura, MD, PhD[b], Hiroaki Ida, MD, PhD[b], Masahiro Nakashima, MD, PhD[g], Toshiyuki Nakayama, MD, PhD[g], Tomayoshi Hyashi, MD, PhD[h], Katsumi Eguchi, MD, PhD[b] and Shigeru Kohno, MD, PhD[a]

S.H. and T.H. contributed equal to this work.

[a]Second Department of Internal Medicine, Nagasaki University School of Medicine, Nagasaki, Japan
[b]Unit of Translational Medicine, Department of Immunology and Rheumatology, Graduate School of Biomedical Sciences, Nagasaki, Japan
[c]Department of Respiratory Disease, University of Occupational and Environmental Health, Fukuoka, Japan
[d]Department of Dermatology, Kanazawa University Graduate School of Medical Science, Ishikawa, Japan
[e]Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan
[f]Department of Internal Medicine, Isahaya Health Insurance General Hospital, Nagasaki, Japan
[g]Department of Tumor and Diagnostic Pathology, Atomic Bomb Disease Institute, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan
[h]Department of Pathology, Nagasaki University Hospital, Nagasaki, Japan

Short running title: IMAM examined by clinical, serologic and MRI study

Address correspondence to:

[*]Hiroshi Mukae, MD, PhD
Professor,
Department of Respiratory Disease,

University of Occupational and Environmental Health, Japan,
1-1 Iseigaoka, Yahata-nishi-ku, Kitakyusyu, Fukuoka 807-8555, Japan
e-mail: hmukae@med.uoeh-u.ac.jp

Key Indexing Terms: IMAM, MAS, myositis-specific autoantibodies, MRI

Abstract

We have introduced the first 3 cases of inflammatory myopathy with abundant macrophages (IMAM) from Asian countries. IMAM was diagnosed based upon the infiltration of CD68+ macrophages into the biopsied specimens, especially the fascia. Proximal skeletal muscle symptoms and signs, elevation of creatin kinase (CK) and myogenic change in electromyography (EMG) were found in all the cases and magnetic resonance imaging (MRI) clearly revealed the thickening of fascia. Since dermatomyositis (DM)-specific skin alterations were not found in the present cases, none of the patients fulfilled the Bohan and Peter's criteria for DM whereas anti-PL-7 antibody was detected in case 1. In addition, CD20+ B-cell infiltration into the fascia was also demonstrated in all the cases, indicating that further transition to DM could be indicated. Severe illness of macrophage activation syndrome（MAS) and acute respiratory distress syndrome (ARDS) complicated in case 1 which resolved by intensive combination therapy. Other 2 cases also required for glucocorticoid for remission.

Abbreviations

anti-ARS Abs: anti-aminoacyl tRNA synthetase antibodies
anti-CADM-140kD Abs: anti-clinically amyopathic dermatomyositis-140kD polypeptide antibodies
anti-155kD/140kD Abs: anti-155kD/140kD polypeptide antibodies
ARDS: acute respiratory distress syndrome
CHP: cytophagic histiocytic panniculitis
CK: cretin kinase
CT: computed tomography
DM: dermatomyositis
EMG: electromyography
IMAM: inflammatory myopathy with abundant macrophages
MAS: macrophage activation syndrome
MRI: magnetic resonance imaging

STIR: short-time inversion recovery
TNF α: tumour necrosis factor α
soluble TNR receptor: sTNFR

Introduction

In addition to the classical inflammatory myopathies, i.e. polymyositis, dermatomysitis (DM) and inclusion body myositis, the spectrum of inflammatory myopathies has recently expanded, especially concerning inflammatory myopathy with predominance of macrophages into the tissues, i.e. macrophagic myofasciitis and inflammatory myopathy with abundant macrophages (IMAM) (1-3). Clinically, IMAM is unrelated to aluminium hydroxide-adjuvanted vaccines and characterized by scaly DM-like or atypical non-DM-like skin alterations and proximal muscle weakness, thus, leading to the clinical diagnosis of DM, atypical systemic lupus erythematosus or overlap syndrome (1-3). Histologically, infiltration of macrophages into the fascia, rather than muscle, is characteristic for IMAM (1-3). A relationship and even a continuum between DM and IMAM is suggested in a case report (2), however, it remains unclear whether IMAM is distinct or not from DM (1-3). This is a first report of IMAM from Asian countries. Furthermore, our report contains new informations regarding to myositis-specific autoantibodies and magnetic resonance imaging (MRI) of the affected tissues in patients with IMAM.

Case report

Table 1 summarized demography of the present 3 cases. Diagnosis of IMAM was based upon the infiltration of CD68+ macrophages into the biopsied specimens (Fig. 1). They had not been received vaccines containing aluminum hydroxide. Since DM specific skin alternations, including heliotrope erythema, Gotron's papuls and Gotron's signs, were not found in all of 3 cases, our present cases did not fulfill Bohan and Peter's criteria for DM (4, 5). Figure 1 shows muscle biopsy specimens of 3 cases. Thickening of fascia was determined in all of biopsied specimens (Fig. 1). A number of CD68+ macrophages associated with CD4+ T-lymphocytes (Fig.1), CD8+ T-lymphocytes (Fig. 1) and CD20+ B-cells (Fig. 1), but few inflammatory cells in the muscle tissue.

Figure 2 A-C show short-time inversion recovery (STIR; TR 3000, TE 12, T1 160) images in plain MRI of the affected muscles. The thickening of fascia was clearly demonstrated by MRI whereas STIR high legions were not so obvious in the muscle tissue. These alternations in MRI reflect similarly the changes found by the histological

study. Myogenic change of the affected muscles was determined in all the 3 cases (data not shown).

Analysis of myositis-specific autoantibodies of anti-aminoacyl tRNA synthetase (ARS) antibodies, anti-clinically amyopathic dermatomyositis -140kD polypeptide antibodies (anti-CADM-140 Abs) and anti-155kD/140kD polypeptide antibodies (anti-155/140kD Abs) was performed in the present cases as we recently reported (6, 7). As shown in Fig. 2D, anti-PL-7 antibody (Ab) was detected in sera from case 1 whereas none of other myositis-specific autoantibodies was found in all of 3 cases. Anti-U1 RNP Ab was detected in case 3 (Fig. 2D).

We briefly described a clinical course of case 1 who complicated with cytophagic histiocytic panniculitis (CHP) of both upper and lower extremities at clinical examination. High serum fibrin degradation products (171 μg/ml), D-dimer (131.4 μg/ml) and ferritin (12,786 ng/ml; normal range, 4.0-87.0 ng/ml) were demonstrated at admission. A computed tomography (CT) scan of the chest showed diffuse consolidation and ground glass opacities throughout both lungs (Fig. 2E). Cell findings of bronchoalveolar lavage fluid revealed a normal appearance, but increased neutrophils (30%) and lymphocytes (25%), which were suggestive as a pattern of diffuse alveolar damage. The bone marrow smear showed normal cellularity with several hemophagocytic macrophages. Thus, in addition to CHP, this patient was considered to suffer from macrophage activation syndrome（MAS) and acute respiratory distress syndrome (ARDS). MAS [This case met the diagnostic criteria for MAS (8) as well as ARDS (9)]. Intensive combination therapy, including plasmapheresis (four times), leukocytapheresis (two times), polymyxin B immobilized fiber direct hemoperfusion (once), pulse methylprednisolone (four times after referral, a total of six times), sivelestat sodium (250 mg/day for 14 days), and oral administration of immunosuppressants (tacrolimus at first, changed to cyclosporine A), was initiated. These therapies were highly effective and most of the above abnormalities recovered within 2 weeks. High serum tumour necrosis factor α (TNF-α), soluble TNR receptor 1 (sTNFR1), and sTNFR2 levels were determined before the treatment [TNF-α = 131.8 pg/ml (11.9 ± 6.4 pg/ml from 16 healthy controls), sTNFR1 = 7.0 ng/ml (1.2 ± 1.1 ng/ml from 13 healthy controls), sTNFR2 = 30.9 ng/ml (3.0 ± 1.3 ng/ml from 13 healthy controls)］which rapidly reduced at 2 weeks later (TNF-α reduced to 20.7 pg/ml, sTNFR1 reduced to 4.2 ng/ml, and sTNFR2 reduced to 14.8 ng/ml). Spontaneous remission was not also demonstareted in case 2 and case 3, and glucocorticoid required for the remission (Table 1).

Discussion

IMAM is recently described from European countries that have reported to resemble with DM (1-3). Our present 3 cases are first report of IMAM from Asian countries. All of our cases represented proximal skeletal muscle symptoms and signs as well as elevation of CK, however, are not fulfilled with Bohan and Peter's criteria for DM. That may follow the previous reports that IMAM is sometimes defined as atypical DM clinically (1-3). It is interesting to note that our present 3 cases show the efficacy of plain MRI to identify thickening of fascia which almost reflects upon the histological finding. Predominant inflammation in the fascia rather than muscle is a characteristic of IMAM (1-3). Plain MRI is a non-invasive method, thus, we recommend plain MRI for early recognition of IMAM.

Severe illness was induced in case 1 due to MAS which is consistent with previous report that IMAM patient was dead from hemophagocytic syndrome and disseminated intravascular coagulopathy (1). High TNF-related cytokines are believed to reflect the activation status of macrophage-lineage cells (10). High serum concentrations of TNF-α, sTNFR1 and sTNFR2 was demonstrated in case 1 before treatment that was rapidly decreased by intensive combination therapy. These data really indicate that macrophages critically involve in the pathologic process of IMAM.

Brunn et al. have compared the cellular subset in affected tissues of IMAM with DM (3). They have found that the difference, i.e., few infiltration of B-cells and plasmatoid dendritic cells whereas more TNF-α producing cells in IMAM as compared with DM (3). Brunn et al. have explained that the difference may reflect the two stages of one disorder or two distinct disease entities. From this point of view, we have evaluated the present 3 cases. All 3 cases have been screened by myositis-specific autoantibodies of anti-ARS antibodies, anti-CADM-140 Abs and anti-155/140kD Abs, respectively which is the first time study for IMAM. Similarity of IMAM of the present cases with DM could be suspected since case 1 expresses anti-PL-7 Ab and infiltration of B-cells into the fascia is found in all of 3 cases. Difference of B-cell infiltration into the fascia in patients with IMAM could be derived from the racial difference. Yamasaki et al. have examined the characteristic of anti-PL-7 Ab-positive DM patients from Japanese population and reported that these patients are milder in skeletal muscle involvement as compared with anti-Jo-1 Ab-positive patients (11), again indicating the development of atypical DM further in case 1. Further clinical evaluation, in either case, are necessary to answer the questions.

Figure Legends

Figure 1. Histologic examination of the present study. A-F; Case 1, a prominent cellular inflammation was found in the fascia. A; control staining by IgG (original magnification, 100 x) B; anti-CD68 monoclonal antibody (mAb) (original magnification, 100 x) C; anti-CD68 mAb (original magnification, 400 x) D; anti-CD4 mAb (original magnification, 100 x) E; anti-CD8 mAb (original magnification, 100 x) F; anti-CD20 mAb (original magnification, 100 x). Remarkable infiltration of CD68+ macrophages, along with CD4+ T-lymphocytes, CD8+ T-lymphocytes and CD20+ B-cells were found. G and H; Case 2, a prominent cellular inflammation was found in the fascia. G; Hematoxylin and eosin staining (original magnification, 100 x) H; anti-CD68 mAb (original magnification, 100 x). I; Case 3, a prominent cellular inflammation of macrophages was found in the fascia. I; anti-CD68 mAb (original magnification, 200 x).

Figure 2. MRI of muscle, chest CT and silver staining of tRNA immunoprecipitated with sera of the present study. Plain STIR MRI of case 1 (A; right brachial muscle), case 2 (B; right quadriceps muscle) and case 3 (C; right quadriceps muscle) before therapy. Arrows indicate the sites of thickening of fascia. D; Plain chest CT of case 1 before therapy shows diffuse consolidation and ground glass opacities throughout both lungs. E;. Silver staining of tRNA immunoprecipitated with sera as described in the text ( ). Lane 1 and 7; total RNA, Lane 2; anti-U1 RNP Ab-positive control serum, Lane 3; Serum of case 3, anti-U1 RNP Ab positive. Lane 4; Serum of case 2, negative. Lane 5; anti-PL-7 Ab-positive control serum, Lane 6; Serum of case 1, anti-PL-7 Ab positive.

References

1.Bassez G, Authier F-J, Lechapt-Zalcman E, Delfau-Larue ME, Plonquet A, Coquet M, et al. Inflammatory myopathy with abundant macrophages (IMAM): a condition sharing similarities with cytophagic histiocytic panniculitis and distinct from macrophagic myofasciitis. J Neuropathol Exp Neurol 2003; 62: 464-74.

2.Carrera E, Lobrinus JA, Spertini O, Gherardi RK, Kuntzer T. Dermatomyositis, lobar panniculitis and inflammatory myopathy with abundant macrophages. Neuromuscul Disord 2006; 16: 468-71.

3.Brunn A, Hans VJ, Vogelgesang S, Deckert M. Inflammatory myopathy with abundant macrophages and dermatomyositis: two stages of one disorder or two distinct entities? Acta Neuropathol 2009 Jul 10. [Epub ahead of print]

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

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

6.Fujikawa K, Kawakami A, Kaji K, Fujimoto M, Kawashiri S, Iwamoto N, et al. Association of distinct clinical subsets with myositis-specific autoantibodies towards anti-155/140-kDa polypeptides, anti-140-kDa polypeptides, and anti-aminoacyl tRNA synthetases in Japanese patients with dermatomyositis: a single-centre, cross-sectional study. Scand J Rheumatol 2009 May 14:1-5. [Epub ahead of print]

7.Mukae H, Ishimoto H, Sakamoto N, Hara S, Kakugawa T, Nakayama S, et al. Clinical Differences Between Interstitial Lung Disease Associated With Clinically Amyopathic Dermatomyositis and Classical Dermatomyositis. Chest. 2009 Jul 6. [Epub ahead of print]

8.Emmenegger U, Schaer DJ, Larroche C, Neftel KA. Haemophagocytic syndromes in adults: current concepts and challenges ahead. Swiss Med Wkly 2005; 135: 299-314.

9.Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994; 149(3 Pt 1): 818-24.

10.Ma X. TNF-alpha and IL-12: a balancing act in macrophage functioning. Microbes Infect 2001; 3: 121-9.

11. Yamasaki Y, Yamada H, Nozaki T, Akaogi J, Nichols C, Lyons R, et al. Unusually high frequency of autoantibodies to PL-7 associated with milder muscle disease in Japanese patients with polymyositis/dermatomyositis. Arthritis Rheum 2006 Jun; 54: 2004-9.

Figure 1

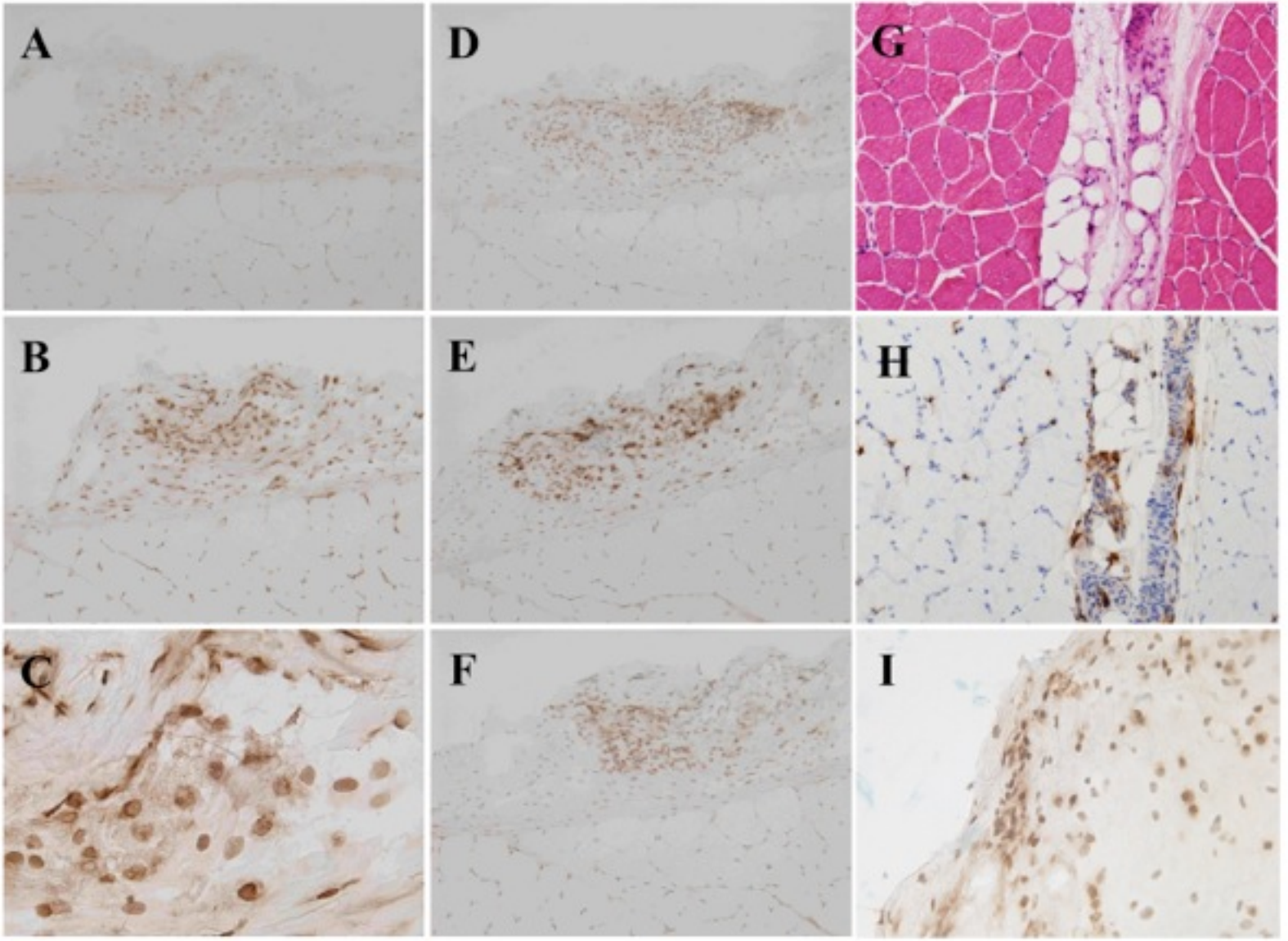

Figure 2

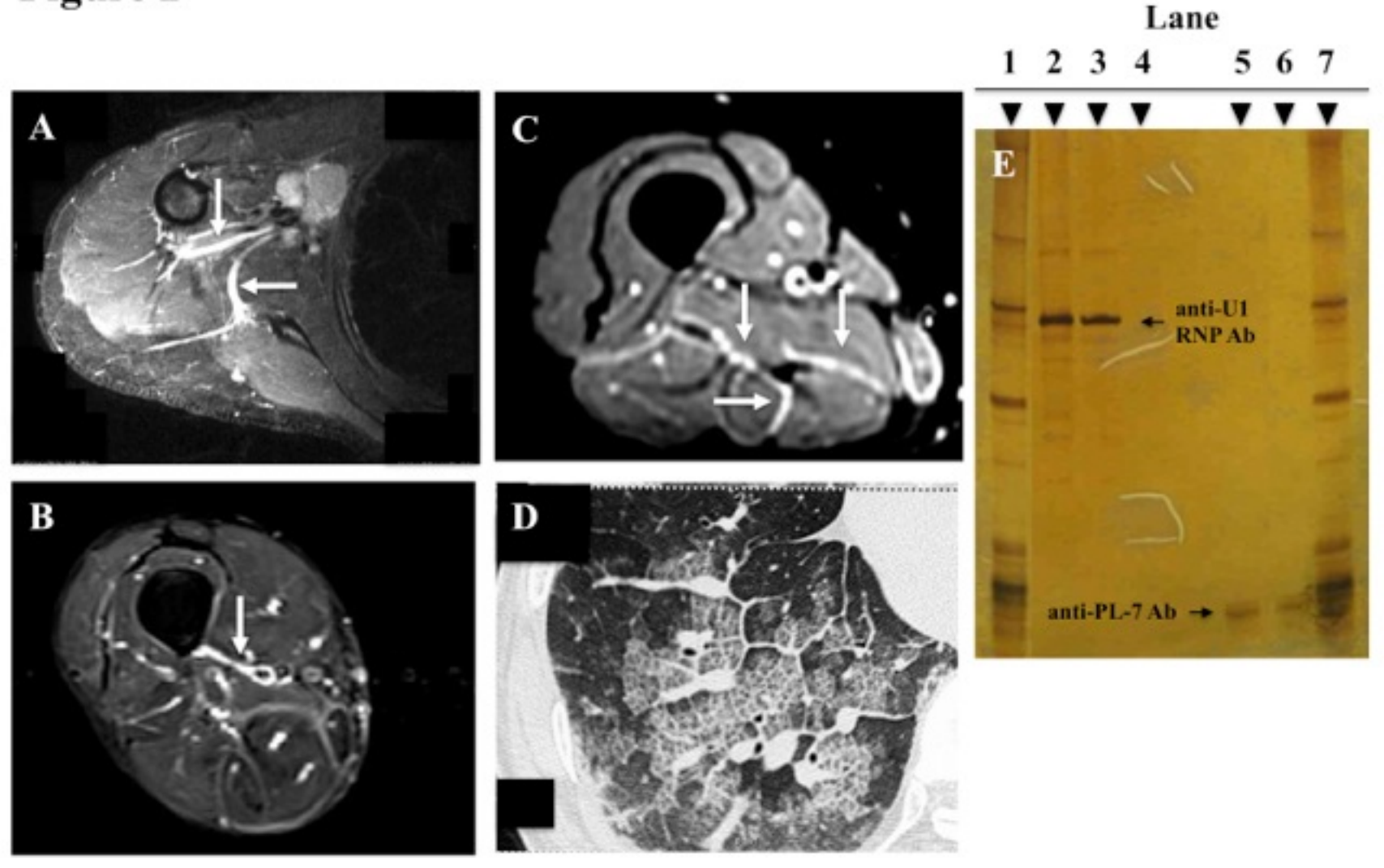

Table 1. Demographic feature of 3 patients with IMAM

Items	Case 1	Case 2	Case 3
Age / Gender	45 y.o. / Female	55 y.o. / Female	58 y.o. / Male
Muscle symptoms			
Myalgia	+	+	+
Weakness	+	+	+
Skin lesions			
Heliotrope erythema	-	-	-
Gotron's papuls	-	-	-
Gotron's signs	-	-	-
Others	Erythema of extremities, CHP	Erythema of hand	Erythema of extremities
Myositis-specific Abs	anti-PL-7 Ab	-	-
Myogenic change in electromyography	+	+	+
Bohan & Peter's criteria	-	-	-
Therapy	Intensive combination	Prednisolone	Prednisolone