

Polymyositis with scleroderma-like features and an anti-PM-Scl75 antibody detected by line blot but not by protein array or immunoprecipitation: A case report and literature review

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ABSTRACT

Anti-PM-Scl antibodies (Abs) are associated with systemic sclerosis (SSc)-myositis overlap syndrome. However, anti-PM-Scl75/100 reactivity detected by line blot (LB) assays is frequently not confirmed by protein array or immunoprecipitation, indicating that such results should be interpreted with caution in Japan. A 72-year-old woman developed limb fatigue and Raynaud's phenomenon, followed by muscle weakness, elevated serum creatine kinase levels, and gangrenous changes in several fingers. Magnetic resonance imaging and muscle biopsy findings were consistent with myositis. She tested positive for antinuclear Abs with a speckled pattern. LB testing showed strong anti-PM-Scl75 reactivity, and fingertip ulcers raised suspicion of SSc-spectrum manifestations. Treatment with prednisolone (25 mg/day) and high-dose intravenous immunoglobulin improved the muscle enzyme elevation and digital lesions. However, anti-PM-Scl75 Abs were not detected by either protein array or immunoprecipitation. The final clinical diagnosis was polymyositis with SSc-spectrum features. We therefore reviewed previously reported cases in which anti-PM-Scl Abs were detected by LB but were not confirmed by other assays. This case demonstrates that myositis with SSc-like clinical manifestations may occur even when anti-PM-Scl75 reactivity is detected only by LB assay. Although autoantibody testing may aid in the diagnosis of myositis, the results should be interpreted in light of the analytical characteristics of each assay. In particular, anti-PM-Scl75/100 reactivity detected by LB should be interpreted with caution when the antinuclear antibody staining pattern is not nucleolar.

KEYWORDS Anti PM-Scl antibody; polymyositis; overlap syndrome; false positivity; immunoprecipitation

Introduction

Anti-PM-Scl75/100 antibodies (Abs) are primarily associated with systemic sclerosis (SSc)-myositis overlap syndrome. In Japan, however, immunoprecipitation (IP)-confirmed anti-PM-Scl75/100-positive myositis is rare, with only four reported cases, including one case of SSc-myositis overlap syndrome [1, 2]. This rarity may partly reflect ethnic differences in Human Leukocyte Antigen (HLA)-DR3 prevalence [3]. An IP assay is considered necessary to confirm these Abs but is not routinely available at general institutions because it requires radioisotopes. Therefore, anti-PM-Scl75/100 Ab is often measured using a line blot (LB) (EUROLINE, Euroimmun Japan Co., Ltd) or protein array (A-Cube[®], Fushimi Pharmaceutical Co., Ltd) assays. However, Japanese studies have reported that many samples positive by LB are negative by IP, indicating false-positive LB results [4].

We encountered a patient with myositis and scleroderma-like manifestations who had strong anti-PM-Scl75 positivity

by LB but negative results by protein array and IP assays. Because similar discordant results may occur in Japanese patients with myositis and/or scleroderma-like manifestations, we describe the assay findings in this case and review previously reported cases.

Case presentation

A woman in her 60s underwent a right upper lobectomy for lung adenocarcinoma (pT2aN0M0, Stage Ib). Three years later, she developed swelling and tenderness in several joints, including the fingers and toes of both hands and feet. At another hospital, the anti-CCP Ab level was 94.8 U/ml, and the rheumatoid factor level was 233 IU/ml. She was diagnosed with rheumatoid arthritis (RA), and methotrexate (6 mg/week) was initiated. On April 28, treatment with the tumour necrosis factor (TNF) inhibitor, golimumab (100 mg/4 weeks), was initiated; thereafter, low disease activity was maintained. Later, an elevated

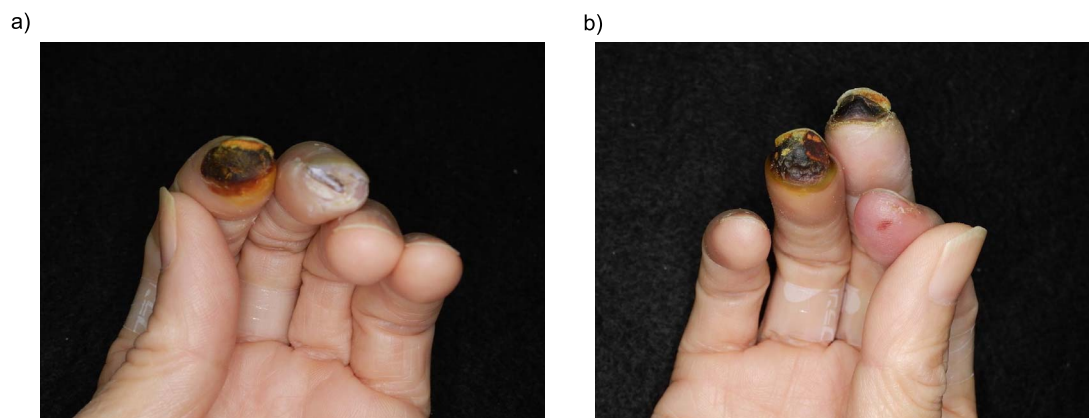


Figure 1. Ulcers on both fingertips prior to treatment: (a) phalangeal ulcer of the left second and third fingers, (b) phalangeal ulcer of the right third and fourth fingers.

carcinoembryonic antigen level was noted, and positron emission tomography–computed tomography (CT) revealed mediastinal lymph node metastasis and pleural dissemination of the lung adenocarcinoma. Methotrexate and golimumab were discontinued, and treatment with osimertinib mesylate (80 mg/day) was initiated. In the following year, CT revealed multiple intrapulmonary metastases. Therefore, golimumab was discontinued and chemotherapy was initiated soon thereafter. However, the intrapulmonary metastases increased, and the disease progressed. Immune checkpoint inhibitors were not administered during the clinical course.

Approximately six months later, the patient developed fatigue in the extremities and Raynaud's phenomenon in both hands. Manual muscle testing revealed grade 4 muscle weakness in the biceps brachii, brachioradialis, iliopsoas, and biceps femoris, and the creatine kinase (CK) level was elevated to 162 U/l. Three months later, she developed necrotic black discoloration of the right third and fourth fingers and the left second and third fingers (Figure 1(a,b)). Anti-SS-A and anti-SS-B Abs were detected, and the Schirmer test showed values of 0 and 2 mm on the right and left sides, respectively. Lip biopsy revealed infiltration of lymphocytes and plasma cells into the stroma. The patient was diagnosed with Sjögren's disease (SjD). Four months later, at 72 years of age, she was admitted to our department for further evaluation.

On admission, no Gottron's or inverse Gottron's sign, periungual erythema, or puffy fingers were observed. Localised skin induration, corresponding to a modified Rodnan skin score of 2, was observed on the anterior aspects of both lower legs. However, skin thickening extending proximally from the fingers or toes was not observed. Neurological and muscle strength evaluations revealed weakness on manual muscle testing (right and left) of the deltoid (5-, 5-), biceps brachii (4, 4), brachioradialis (4, 4), iliopsoas (4, 4), and biceps femoris (5-, 4). However, strength was preserved in the triceps brachii, finger flexors, intrinsic hand muscles, lumbrical muscles, gastrocnemius, and tibialis anterior, and no sensory disturbances were observed. The blood test results are presented in Table 1. Serum levels of CK, 854 U/l; aspartate aminotransferase (AST), 75 U/l; and lactate dehydrogenase, 537 U/l, indicated an elevation in myogenic enzymes, and Immunoglobulin G (IgG) was elevated to 3420 mg/dl. Chest CT revealed no obvious interstitial lung disease (Figure 2(a)). Magnetic resonance imaging (MRI) revealed mild hyperintensity in the right rectus femoris and vastus lateralis on

T2-weighted images (Figure 2(b)). A biceps brachii muscle biopsy showed degeneration and regeneration of muscle fibres on haematoxylin and eosin (H&E) staining (Figure 2(c)). C5b9 (Figure 2(d)) and major histocompatibility complex staining (Figure 2(e)) were negative and positive, respectively.

The antinuclear antibody (ANA) titer by indirect immunofluorescence assay was 1:160, with a speckled pattern but no nucleolar pattern. Physical findings and blood test results strongly suggested myositis; however, routine tests for myositis-associated Abs were negative (Table 1). Therefore, additional autoantibodies were examined using the LB assay (EUROLINE), and only anti-PM-Scl75 Ab was strongly positive (3+). Other positive autoAbs included anti-CCP, anti-SS-A/SS-B, and anti-SS-B (Table 1). Both the protein array assay (A-Cube®) and the IP assay subsequently performed at Kyoto University showed negative results for anti-PM-Scl75 Ab.

According to the 2016 ACR/EULAR classification criteria, the patient fulfilled the criteria for SjD, scoring 7 points based on labial salivary gland histopathology, anti-SS-A positivity, and Schirmer test positivity. Under the 2017 ACR/EULAR classification criteria for idiopathic inflammatory myopathies, she scored 5.6 points based on age ≥ 40 years, progressive symmetric proximal muscle weakness of the upper and lower limbs; elevated serum CK/LDH/AST/ALT levels, and mononuclear cell infiltration in the perimysium and perivascular areas. According to the revised Ministry of Health, Labour and Welfare diagnostic criteria for polymyositis/dermatomyositis, she fulfilled the criteria for polymyositis based on proximal muscle weakness, predominantly in the upper or lower limbs, elevated serum myogenic enzyme levels; electromyographic changes; systemic inflammatory findings; and muscle biopsy findings. Regarding SSc, the patient scored 5 points based on fingertip ulcers and Raynaud's phenomenon and therefore did not meet the ACR/EULAR classification criteria. Under the diagnostic criteria of the Ministry of Health, Labour and Welfare, she met only the criterion for fingertip ulcers and did not fulfil the diagnostic criteria. The skin induration on the anterior aspects of both lower legs was not accompanied by skin thickening of the fingers or toes; therefore, it could not be definitively attributed to SSc and was not included in the diagnostic criteria. Based on these findings, anti-PM-Scl Ab positivity detected by the LB assay was ultimately considered a false-positive result, and the patient was diagnosed with polymyositis with features of the SSc spectrum, in addition to RA and SjD.

Table 1. Laboratory blood tests.

Haematology		Reference range	Autoantibodies	Reference range	
White blood cells	4300/ μ l	3300–8600/ μ l	ANA (IFA)	1:160	<1:40
Haemoglobin (Hb)	11.0 g/dl	11.6–14.8 g/dl	Homogeneous pattern	Negative	Negative
Platelet count	185,000/ μ l	158,000–348,000/ μ l	Speckled pattern	1:160	Negative
Coagulation			Nucleolar pattern	Negative	Negative
Activated partial thromboplastin time	26 sec	24–40 sec	Peripheral pattern	Negative	Negative
Prothrombin time	11 sec	11–13 sec	Discrete speckled pattern	Negative	Negative
Fibrinogen	409 mg/dl	160–350 mg/dl	Cytoplasmic pattern	Negative	Negative
D-dimer	2.1 μ g/ml	<1.0 μ g/ml	Anti-centromere Ab	< 0.4 U/ml	<7.0 U/ml
Biochemistry			Anti-U1-RNP Ab	1 U/ml	<3.5 U/ml
Total Protein	8.6 g/dl	6.6–8.1 g/dl	Anti-Sm Ab	< 0.7 U/ml	<7.0 U/ml
Albumin	3.6 g/dl	4.1–5.1 g/dl	Anti-SS-A Ab	> 240 U/ml	<7.0 U/ml
Globulin	5.0 g/dl	2.2–3.4 g/dl	Anti-SS-B Ab	130.8 U/ml	<7.0 U/ml
CK	854 U/l	41–153 U/l	Anti-Jo-1 Ab	< 0.3 U/ml	<7.0 U/ml
CK-MB	46 U/l	<12 U/l	Anti-RNA Polymerase III Ab	< 5.0	<28
AST	75 U/l	13–30 U/l	Anti-topoisomerase I Ab	< 0.6 U/ml	<7.0 U/ml
ALT	40 U/l	7–23 U/l	Anti-ARS Ab	9.5	<25
LDH	537 U/l	124–222 U/l	Anti-MDA5 Ab	Negative	<32
Alkaline phosphatase	73 U/l	38–113 U/l	Anti-TIF1- γ Ab	Negative	<32
γ -GTP	21 U/l	9–32 U/l	Anti-Mi-2 Ab	Negative	<53
Creatinine	0.52 mg/dl	0.46–0.79 mg/dl	Anti-Cardiolipin IgG Ab	$\leq$ 2.6 U/ml	$\leq$ 20.0 U/ml
eGFR	85.9 ml/min/1.73 m ²	$\geq$ 60 ml/min/1.73 m ²	Anti-Cardiolipin IgM Ab	4.3 U/ml	$\leq$ 20.0 U/ml
Blood urea nitrogen	16.5 mg/dl	8–20 mg/dl	Anti- β 2 Glycoprotein I IgG Ab	$\leq$ 6.4 U/ml	<20.0 U/ml
Sodium (Na)	137 mEq/l	138–145 mEq/l	Anti- β 2 Glycoprotein I IgM Ab	1.2 U/ml	$\leq$ 20.0 U/ml
Potassium (K)	4.0 mEq/l	3.6–4.8 mEq/l	Anti-DNA Ab	5.9 IU/ml	$\leq$ 6.0 IU/ml
Chloride (Cl)	103 mEq/l	101–108 mEq/l	[Line blotting]		
Calcium (Ca)	8.6 mg/dl	8.8–10.1 mg/dl	Anti-Ku Ab	Negative	Negative
Inorganic phosphorus (IP)	4.2 mg/dl	2.7–4.6 mg/dl	Anti-PM-Scl100 Ab	Negative	Negative
B-type natriuretic peptide	45.1 pg/ml	18.4 pg/ml	Anti-PM-Scl75 Ab	3+	Negative
KL-6	324 U/ml	105.3–401.2 U/ml	Anti-SRP Ab	Negative	Negative
C-reactive protein	0.09 mg/dl	<0.14 mg/dl	Anti-Jo-1 Ab	Negative	Negative
Immunoglobulins			Anti-PL-7 Ab	Negative	Negative
IgG	3420 mg/dl	861–1747 mg/dl	Anti-PL-12 Ab	Negative	Negative
IgA	244 mg/dl	93–393 mg/dl	Anti-OJ Ab	Negative	Negative
IgM	220 mg/dl	50–269 mg/dl	Anti-EJ Ab	Negative	Negative
IgE	75 IU/ml	<358 IU/ml	Anti-Ro-52 Ab	Negative	Negative
CH50	41 U/ml	30–46 CH50/ml	[protein array]	(Index value)	
C3	95 mg/dl	73–138 mg/dl	Anti-PM-Scl100 Ab	Negative (1.3)	Negative (<10)
C4	18 mg/dl	11–31 mg/dl	Anti-PM-Scl75 Ab	Negative (3.9)	Negative (<10)
Cryoglobulin	Negative	Negative			

Abbreviations: ANA, antinuclear antibody; IFA, indirect immunofluorescence; Ab, antibody.

The presence of lung adenocarcinoma made the use of immunosuppressive therapy challenging. The patient was treated with prednisolone (25 mg/day) and high-dose intravenous immunoglobulin (20 g/day). After five days of intravenous immunoglobulin therapy, prednisolone monotherapy was continued and gradually tapered according to the clinical course. Although the serum CK level was 475 U/l at the start of treatment, it decreased after treatment initiation and normalised to 82 U/l on day 46. Prednisolone was subsequently tapered, and the serum CK level remained within the normal range. Regarding the skin findings, the gangrenous tissue spontaneously desquamated, with no further progression and gradual improvement over time (Figure 3(a,b)). At the final follow-up, the prednisolone dose had been reduced to 4 mg/day.

Discussion

Reports from Japan have described false-positive cases in which anti-PM-Scl75/100 Abs are positive by LB but negative by IP [4]. However, this discrepancy may not be widely

recognised, and its cause remains unclear. In the present case, the anti-PM-Scl75 Ab result by LB was considered a false-positive result; however, the patient was diagnosed with polymyositis with scleroderma-like symptoms in addition to RA and SjD.

Here, we discuss the characteristics of false-positive cases with anti-PM-Scl75/100 Ab positivity by LB. Table 2 summarises previously reported cases with anti-PM-Scl75/100 Ab positivity, including protein and IP assays, ANA patterns, other concurrently measured autoAbs, and clinical characteristics. Among the 10 cases (including the present case) that were positive by LB but negative by protein array or IP, four lacked a nucleolar ANA pattern. Anti-PM-Scl Abs target nucleolar antigens and generally produce a nucleolar pattern. Therefore, the absence of a nucleolar pattern may suggest false positivity. In the present patient, ANA testing showed a speckled pattern without a nucleolar pattern. However, anti-PM-Scl Ab positivity confirmed by IP has been reported in a patient with only a speckled pattern [1]; therefore, false positivity cannot be determined solely from the absence of a nucleolar pattern. Regarding clinical manifestations, the

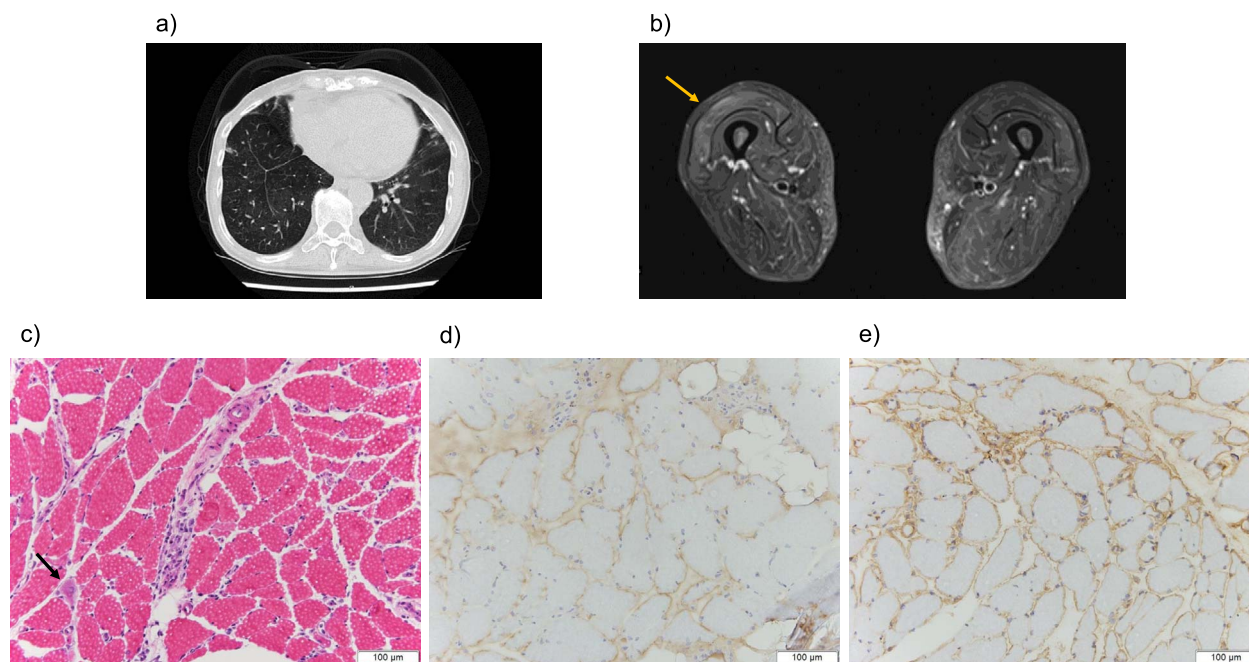


Figure 2. Imaging and pathological examinations: (a) chest CT, (b) thigh MRI T2-weighted image on admission, and muscle biopsy findings; (c) H&E staining: degeneration and regeneration of muscle fibres are observed in the area indicated by the arrow; (d) C5b9-staining; and (E) MHC-staining.

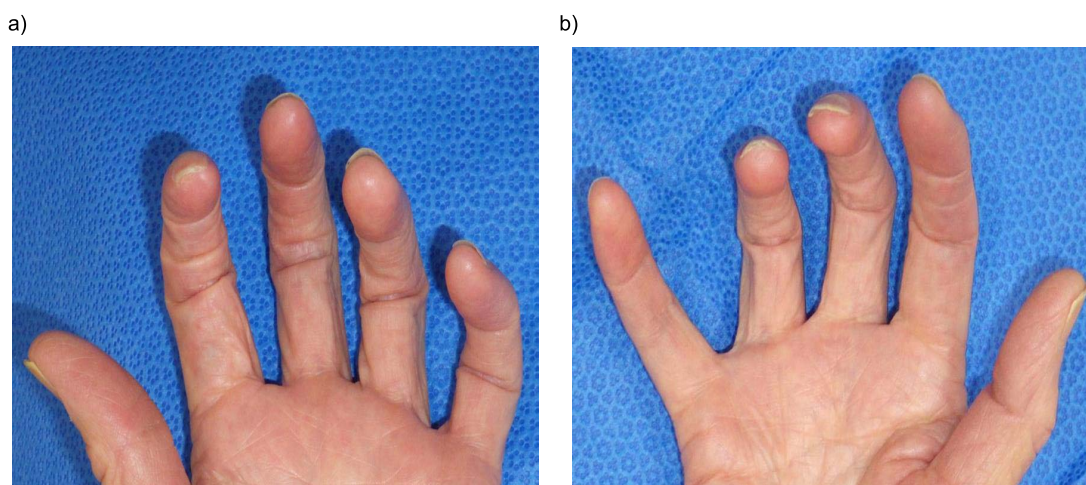


Figure 3. Improvement in ulcers on the tips of both fingers: (a) improvement of the left finger ulcer following treatment, (b) improvement of the right finger ulcer following treatment.

prevalence of pulmonary hypertension was higher in cases in which anti-PM-Scl75/100 Ab positivity was confirmed by IP (14.0% vs. 0%), but no clear differences were found in other clinical findings (Table 2). Pulmonary hypertension may therefore support anti-PM-Scl Ab positivity. Other anti-PM-Scl Ab-positive patients with skin ulcers and myositis similar to those in our patient have been reported [4]. However, unlike our patient, these cases had autoAbs strongly associated with SSc or myositis and corresponding clinical manifestations, such as anti-topoisomerase I, anti-U3RNP, and anti-Ku Abs.

The IP and LB assays may detect Abs directed against different epitopes of the PM-Scl antigen. Because LB assays use denatured proteins, they may not detect Abs that recognise conformational epitopes, whereas IP assays detect Abs that react with native protein structures [4]. In the present case, the Ab detected by LB may have reacted with denatured

nuclear proteins; however, it remains unclear whether the target was a true PM-Scl75/100 epitope. An earlier study examined the clinical features of 10 patients with antisynthetase Ab syndrome who were positive by enzyme-linked immunosorbent assay but negative by IP and found that all had lung lesions and six (53%) had interstitial lung disease [5]. The possibility that these Abs inhibit RNA-aminoacyl-tRNA synthetase binding or bind to denatured aminoacyl-tRNA synthetase has also been suggested [5].

Among cases positive for anti-PM-Scl75/100 Abs by LB, few were retested by IP or protein array, leaving insufficient data to compare the clinical characteristics of true anti-PM-Scl Ab-positive and false-positive cases. The 108 cases that were not confirmed by IP or protein array may have included some false-positive results, preventing a clear assessment of differences in test findings or clinical symptoms (Table 2)

Table 2. Immunological and clinical characteristics in cases with anti-PM-Scl antibody positivity determined by LB and/or immunoprecipitation assay.

	n	ANA positivity rate/staining patterns of ANA	Other positive autoAbs	Clinical diagnosis	Raynaud's phenomenon	Calcinosis	Lung fibrosis	Restrictive lung disease	Interstitial pneumopathy	Pulmonary Hypertension	Muscle weakness	Scleroderma	Inflammation-myositis	Inflammation-reference myositis
IP assay positive	57	No data	No data	Diffuse SSc (17) Limited SSc (40) Scleroderma	11 (78.6%)	20 (35.1%)			8 (14.0%)	52 (91.2%)	11 (20.0%)	6		
LB assay positive and IP assay/protein array assay unmeasured	14	No data	No data			3 (21.4%)			3 (21.4%)	10 (71.4%)	7			
	3	No data	No data	ILD and myositis specific and associated autoAbs Diffuse SSc (18)	1 (33%)		16 (55.2%)	18 (62.1%)	3 (100%)		1/2 (50%)	0 (0%)		8
	29	No data	Anti-Topo1 Ab (13), anti-PM-Scl100 Ab (13), anti-CENP-B Ab (2), anti-U1 RNP Ab (2)							2 (6.9%)				9
				Limited SSc (3) Overlap syndromes (6) UCTD (2) SLE (1)										
RA (3)	22	No data	Anti-topo I Ab (5), Anti-centromere Ab (3), CENP B Ab (3), CENPA Ab (2), Anti-RNA polymerase III Ab (4), anti-RNA Polymerase III 11 Ab (3), anti-RNA Polymerase III 155 Ab (2), Anti-fibrillarin Ab (1), Anti-Ku Ab (1), Anti-NOR-90 Ab (1), Anti-Ro52 Ab (4)	Diffuse SSc (7)		6 (27.3%)			13 (59%)	5 (22.7%)			7 (31.8%)	10
	2	Case 1: ×160 (nucleolar), Case 2: ×40 (nucleolar)	No Ab	Limited SSc (15) Dermatomyositis							1 (50%)	1 (50%)		11
	16	Case 1: ×160–640 (nucleolar + speckled), Case 2: ×1280–2560 (mixed homogeneous + nucleolar), Case 3: ×80 (homogeneous + nucleolar chromosome positive), Case 4: ×1280 (nucleolar)	No Ab	Diffuse SSc (4) Limited SSc (12) Idiopathic inflammatory myopathy Case 1: Necrotizing inflammatory myopathy Case 2: Myopathy and SSc		6 (37.5%)			8 (50.0%)	3 (21.4%)		16 (100%)	1 (7.7%)	12
	16	Case 1: ×160–640 (nucleolar + speckled), Case 2: ×1280–2560 (mixed homogeneous + nucleolar), Case 3: ×80 (homogeneous + nucleolar chromosome positive), Case 4: ×1280 (nucleolar)	No Ab	Idiopathic inflammatory myopathy Case 1: Necrotizing inflammatory myopathy Case 2: Myopathy and SSc	11 (68.8%)	0 (0%)	8 (50.0%)		14 (87.5%)		16 (100%)			13
	4	Case 1: ×160–640 (nucleolar + speckled), Case 2: ×1280–2560 (mixed homogeneous + nucleolar), Case 3: ×80 (homogeneous + nucleolar chromosome positive), Case 4: ×1280 (nucleolar)	Case 2: anti-dsDNA Ab, anti-SS-A Ab and anti-SS-B Ab	Case 1: Necrotizing inflammatory myopathy Case 2: Myopathy and SSc	3 (75%)				0/2 (0%)		4 (100%)	3 (75%)	4 (100%)	14
	1	no data	Anti-centromere Ab	Case 3: Myopathy and SSc Case 4: Myopathy and SSc	0 (0%)				1 (100%)		1 (100%)	0 (0%)	1 (100%)	15
	1	×40 (speckled and nucleolar patterns)	No data	Inflammatory myopathy with apparent clinical classification of PM Clinically defined inclusion body myositis	0 (0%)						1 (100%)	0 (0%)	1 (100%)	16
Subtotal LB positive and IP assay/protein array assay negative	108	Case 1: ×80 (Homogenous+Speckled) Case 2: ×1280 (Homogenous+Nucleolar) Case 3: ×1280 (Homogenous+Nucleolar) Case 4: ×1280 (Nucleolar) Case 5: ×160 (speckled)	anti-Topoisomerase 1 Ab (4), anti-U3-RNP Ab (2), anti-Ku Ab (2) anti-RNA polymerase Ab (1) Limited SSc (3)	Diffuse SSc (6)	26 (66.7%)	15 (22.1%)	24 (53.3%)	18 (62.1%)	53 (71.6%) 7 (77.8%)	13 (16.0%)	24 (92.3%)	20 (74.0%)	24 (41.4%) 4 (44.4%)	4
	1	×160 (speckled)	anti-SS-A Ab, anti-SS-B Ab, anti-cyclic citrullinated peptide Ab	Myositis associated with SJD	(+)	(–)	(–)	(+)	(–)	(–)	(+)	(+)	(+)	Current Case
Subtotal	10				1 (100%)	1 (100%)	0 (0%)	1 (100%)	6 (60%)	0 (0%)	1 (100%)	1 (100%)	5 (50%)	

[4, 6–16]. This limitation may reflect both the rarity of anti-PM-Scl Ab-positive patients in Japan and the limited recognition of the high false-positive rate of LB testing for anti-PM-Scl Abs. Further verification of discrepant anti-PM-Scl Ab results by IP or protein array is warranted.

Although the positive anti-PM-Scl Ab result by LB was ultimately considered a false-positive result, Raynaud's phenomenon, digital ulcers, and myositis developed concurrently with the recurrence of lung adenocarcinoma. Digital ischemia and ulceration may occur as paraneoplastic manifestations in patients with dermatomyositis, suggesting that mechanisms related to malignancy and autoimmune inflammation contribute to the development of digital vascular lesions [17]. Therefore, Raynaud's phenomenon, digital ulcers, and myositis observed in the present case may represent manifestations of a paraneoplastic syndrome associated with recurrent malignancy. In addition, cutaneous ulcers secondary to vasculitis associated with RA or SjD were considered in the differential diagnosis. TNF inhibitor-induced manifestations were also considered; however, a causal relationship was considered unlikely given the prolonged interval between discontinuation of TNF inhibitor therapy and the onset of the patient's clinical manifestations. In addition, we considered the possibility of antiphospholipid Abs and cryoglobulinemia, but these were ruled out based on the blood test results.

Conclusion

False-positive anti-PM-Scl75 results by LB may occur even in patients with myositis and scleroderma-like symptoms, as illustrated by the present case. When scleroderma–myositis overlap syndrome is suspected and anti-PM-Scl75/100 Abs are positive by LB, false positivity should be considered, particularly when the ANA pattern is not nucleolar.

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Conflict of interest

None declared.

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Ethical approval

Not applicable.

Patient consent

Written informed consent for publication of this report was obtained from the patient by the corresponding author for publication of this report.

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