Anti-p155/140 Antibody-positive Dermatomyositis with Metastases Originating from an Unknown Site

Masafumi Ohashi[1], En Shu[1], Masataka Tokuzumi[1], Kei Fujioka[2], Tatsuo Ishizuka[2], Akira Hara[3], Manabu Fujimoto[4], Kenzo Kaji[4] and Mariko Seishima[1]*

*Departments of [1]Dermatology, [2]General Internal Medicine, and [3]Tumor Pathology, Gifu University Graduate School of Medicine, Yanagido 1-1 Gifu, and [4]Department of Dermatology, Kanazawa University Graduate School of Medicine, Kanazawa, Japan. *E-mail: marikoseishima@yahoo.co.jp*

Accepted May 25, 2010.

Dermatomyositis (DM) is a systemic inflammatory myopathy with characteristic cutaneous manifestations (a heliotrope rash, Gottron's papules, paronychial erythema and nailfold bleeding) and is often associated with interstitial lung disease and internal malignancy. Thus far, some autoantibodies specific for myositis have been discovered, including antibodies to aminoacyl-tRNA synthetases (ARS), anti-Mi-2 antibodies, anti-CADM 140 antibody, anti-p155/140 antibody and others (1–3). The various autoantibody-positive subgroups of DM vary in their clinical features. Of these myositis-specific autoantibodies, the anti-p155/140 antibody is a 155-kDa reactive nuclear protein relevant to cancer-associated DM (1, 4–8). However, the frequency of malignancies in patients with anti-p155/140 antibody is undefined because no large epidemiological studies have been undertaken. We describe here a patient with anti-p155/140 antibody-positive DM who had a poorly differentiated metastatic adenocarcinoma; however, the primary tumour could not be identified despite comprehensive examination.

CASE REPORT

A 57-year-old man presented with refractory erythema on the hands and face, muscle weakness and dysphagia. Two months before consultation, he had had erythema on the face, which had spread to the precordium and limbs.

At the first presentation the patient had a typical heliotrope rash, Gottron's papules, paronychial erythema, nailfold bleeding and hyperkeratotic erythema over the elbow (Fig. 1). Blood examination revealed a high erythrocyte sedimentation rate (62 mm/h), high levels of lactate dehydrogenase (LDH) (295 IU/l), C-reactive protein (CRP) (8.13 mg/dl), creatine kinase (CK) (863 IU/l; reference values: 50–200 IU/l), myoglobin (240 ng/ml) and aldolase (8.6 U/l). The antinuclear antibody titre was positive at 1:40 with a homogeneous and speckled pattern. As for tumour markers, carcinoembryonic antigen (CEA) was high at 115 ng/ml (reference values: < 5.0 ng/ml). He was later found to be positive for anti-p155/140 antibody by an immunoprecipitation study performed using extracts of the leukaemia cell line, K562 (4, 9) (Fig. 2). Chest computerized tomography (CT) revealed aspiration pneumonia. However, there were no signs of interstitial pneumonia.

Biopsy specimens were obtained from the left deltoid muscle and the Gottron's papule on the fifth metacarpophalangeal joint of the left hand. Histology of the muscle showed inflammatory infiltration of mainly lymphocytes around the muscle fibres. The muscle fibres showed necrotic changes, including size irregularities and reduced staining. The skin biopsy showed hyperkeratosis, thickening of the granular layer, slight lymphocyte infiltration and pigment incontinence at the dermo-epidermal junction.

On the basis of the clinical and pathological findings, we diagnosed this case as DM. Taking into account the high CEA, upper gastrointestinal endoscopy and colonoscopy, hepatic and mammary ultrasonography, systemic contrast-enhanced CT, head magnetic resonance imaging (MRI) and tumour scintigraphy were performed; however, no malignancies were found.

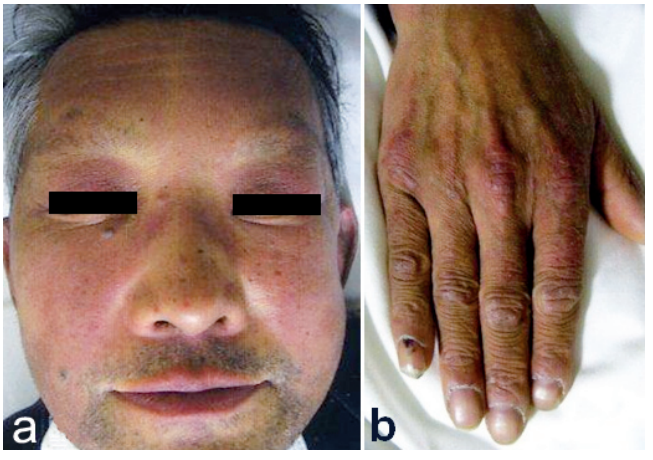

Fig. 1. (a) Heliotrope rash and (b) Gottron's papules, paronychial erythema, and nailfold bleeding were observed on examination.

From initial consultation we started the patient on 60 mg/day of prednisolone and antibiotics for aspiration pneumonia. Since the cutaneous manifestations and muscle weakness improved, we gradually tapered the dose of prednisolone. Although these symptoms did not recur, CEA continued to rise. The systemic PET-CT scan showed abnormal accumulation of fluorine 18 fluorodeoxyglucose (FDG) in the lymph node swelling in the supraclavicular fossa and mediastinum. Therefore, a mediastinal lymph node biopsy was carried out by fine needle aspiration through upper gastrointestinal endoscopy. On haematoxylin and eosin staining, the biopsy showed a poorly differentiated adenocarcinoma. Immunostaining for cytokeratin 7 and thyroid

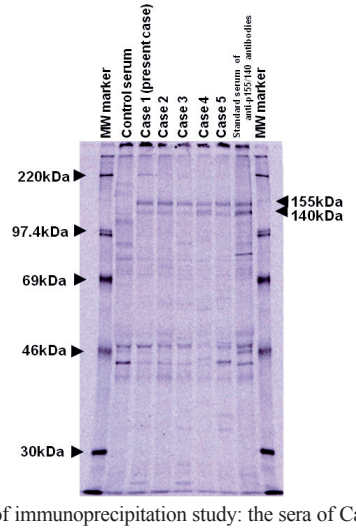

Fig. 2. Results of immunoprecipitation study: the sera of Cases 1–5 immunoprecipitated 155-kDa and 140-kDa bands. See Table I for description of cases.

Table I. *Characteristics of five cases of dermatomyositis with the anti-p155/140 antibody and no interstitial pnemonia*

Case no. Age/sex	Heliotrope rash	Gottron's sign	Serum creatine kinase[a]	Internal malignancy	Anti-nuclear antibody
1. 57/M[b]	+	+	863	Poorly differentiated adenocarcinoma (the primary unidentified)	40× (Hom, Spe)
2. 76/F	–	+	523	Unexamined	80× (Spe)
3. 65/F	–	+	894	Lung (large cell carcinoma)	160× (Hom, Spe)
4. 74/F	+	+	146	Lung (large cell carcinoma)	80× (Hom, Spe)
5. 58/M	+	+	300	Metastatic hepatocarcinoma (the primary unidentified)	80× (Hom, Spe)

[a]Reference values of creatine kinase: 50–200 IU/l. [b]Present case.
Hom: homogeneous type; Spe: speckled typ.

tissue factor-1 (TTF-1) was positive, but immunostaining for cytokeratin 20 was negative. Taking these histological findings into account, we suspected that the primary tumour in our patient was a lung or thyroid carcinoma. Therefore, cervical MRI and bronchoscopy were performed, but failed to show any signs of malignancy in these organs.

One month after the mediastinal lymph node biopsy, bone scintigraphy showed multiple metastases to the ribs. The patient died of a relapse of aspiration pneumonia 2 days after re-hospitalization. Autopsy was not carried out due to non-consent of his family.

DISCUSSION

Anti-p155/140 antibody is an antinuclear antibody that appears in a speckled pattern, and its target is proposed to be transcriptional intermediary factor 1-gamma (10). This autoantibody is strongly relevant to cancer-associated DM (1, 4) and has a high specificity (95.9%) (6). Cancer onset is mostly concomitant with DM or occurs within a year of diagnosis of DM (6). Currently, only the anti-Jo-1 antibody is examined in routine tests concerning DM. Thus, it is necessary to develop a simpler and more widely available test to help precise and early diagnosis of anti-p155/140 antibody-positive DM.

The clinical features of anti-p155/140 antibody-positive myositis are considered to be typical skin eruptions (such as V-sign rash, heliotrope rash and Gottron's papules) and the absence of interstitial pneumonia (1). Moreover, flagellate erythema is the most significant type of skin eruption, and most patients have muscle weakness or elevated serum CK levels (4).

Although flagellate erythema was absent in our patient, the other typical symptoms and absence of interstitial pneumonia were all evident, which along with the continuous increase in CEA levels strongly suggested an internal malignancy. Indeed, we discovered mediastinal lymph node metastases and diagnosed their histological type, but could not identify the primary tumour. The association with anti-p155/140 antibody is reported to be with carcinomas of the stomach, lung, breast and gall bladder (4). The possible primary cancer in our patient was thought to be of the lung, but the diagnosis remains unknown because autopsy was not performed.

In Table I, we have summarized five cases of dermatomyositis positive for the anti-p155/140 antibody (Fig. 2), including the present case, reported in our affiliated hospitals. Although the heliotrope rash was not present in two cases, none of the cases had interstitial pneumonia. All except the one patient who could not be examined had malignant tumours. Four patients with elevated CK levels showed muscle weakness, and the anti-nuclear antibody titres were not very high in any of the cases.

REFERENCES

1. Targoff IN, Mamyrova G, Trieu EP, Perurena O, Koneru B, O'Hanlon TP, et al. A novel autoantibody to a 155-kD protein is associated with dermatomyositis. Arthritis Rheum 2006; 54: 3682–3689.
2. Gunawardena H, Wedderburn LR, North J, Betteridge Z, Dunphy J, Chinoy H, et al. Clinical associations of autoantibodies to a p155/140 kDa doublet protein in juvenile dermatomyositis. Rheumatol 2008; 47: 324–328.
3. Gunawardena H, Betteridge ZE, McHugh NJ. Myositis-specific autoantibodies: therir clinical and pathogenic significance in disease expression. Rheumatol 2009; 48: 607–612.
4. Kaji K, Fujimoto M, Hasegawa M, Kondo M, Saito Y, Komura K, et al. Identification of a novel autoantibody reactive with 155 and 140 kDa nuclear proteins in patients with dermatomyositis: an association with malignancy. Rheumatol 2007; 46: 25–28.
5. Madan V, Chinoy H, Griffiths CEM, Cooper RG. Defining cancer risk in dermatomyositis. Part II. Assessing diagnostic usefulness of myositis serology. Clin Exp Dermatol 2009; 34: 561–565.
6. Chinoy H, Fertig N, Oddis CV, Ollier WE, Cooper RG. The diagnostic utility of myositis autoantibody testing for predicting the risk of cancer-associated myositis. Ann Rheum Dis 2007; 66: 1345–1349.
7. 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; 38: 263–267.
8. Trallero-Araguás E, Labrador-Horrillo M, Selva-O'Callaghan A, Martínez MA, Martínez-Gómez X, Palou E, et al. Cancer-associated myositis and anti-p155 autoantibody in a series of 85 patients with idiopathic inflammatory myopathy. Medicine (Baltimore) 2010; 89: 47–52.
9. Sato S, Hirakata M, Kuwana M, Suwa A, Inada S, Mimori T, et al. Autoantibodies to a 140-kD polypeptide, CADM-140, in Japanese patients with clinically amyopathic dermatomyositis. Arthritis Rheum 2005; 52: 1571–1576.
10. Targoff IN, Trieu EP, Levy-Neto M, Prasertsuntarasai T, Miller FW. Autoantibodies to transcriptional intermediary factor 1-gamma (TIF1-g) in dermatomyositis. Arthritis Rheum 2006; 54: S518 (abstract).