

## SHORT COMMUNICATION

## Pemphigus Foliaceus Associated with Anti-NXP2 Autoantibody-positive Dermatomyositis

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Pemphigus foliaceus (PF) is one of the autoimmune blistering diseases (ABDs) characterised by autoantibodies (Abs) binding to desmoglein (Dsg) 1, resulting in acantholysis and intraepidermal blistering. Several other autoimmune diseases have been reported to occur in patients with ABDs, such as rheumatoid arthritis, systemic lupus erythematosus, and Grave's disease (1). However, ABD associated with dermatomyositis (DM) is rare. We report here the first case in which the Ab of DM is identified.

## CASE REPORT

A 39-year-old Japanese woman with a 4-month history of skin eruptions was referred to our hospital in July 2007. Physical examination showed pruritic malar erythema on the face, including the medial canthi of the eyes and alar part of the nose (Fig. 1A), diffuse alopecia and erythema on the scalp, and Gottron's papules on the dorsum of the hands (Fig. 1B). Muscle weakness and dysphagia were not present, and cutaneous calcinosis was not found. She had no medical history of note. A biopsy specimen from the erythematous lesion on the cheek showed mild basal vacuolar change and sparse superficial perivascular infiltration of lymphocytes. Direct immunofluorescence microscopy revealed no deposition of immunoglobulin or complement. Laboratory investigations showed raised levels of creatine kinase (514 IU/l; normal 45–163) and aldolase (10.7 IU/l; 2.1–6.1). Circulating Abs against Jo-1, SS-A/Ro, and SS-B/La were not detected using enzyme-linked immunosorbent assay (ELISA). Anti-nuclear matrix protein 2 Ab (anti-NXP2 Ab) was identified by immunoprecipitation assay with 35S-labelled K562 cell extracts (2). Biopsy from the left quadriceps femoris muscle

showed no apparent findings of myositis. We diagnosed the patient with clinically amyopathic dermatomyositis (CADM). Screening for internal malignancy and interstitial lung disease was negative. We treated the patient with topical, not systemic, corticosteroids. The skin eruptions of DM gradually improved from April 2008 and had almost disappeared in June 2009. Anti-NXP2 Ab was no longer detected in the sera in June 2011, and DM has not relapsed for 3 years.

In December 2009, she noticed mild erythema on the chest and back. She presented with some erythema and erosions on the chest and back (Fig. 1C) in June 2010. There was no mucous membrane involvement. Histopathological examination of a biopsy specimen showed acantholysis and superficial split in the granular layer (Fig. 1D). Direct immunofluorescence showed intercellular staining for IgG and C3 in the epidermis. Anti-Dsg Ab ELISA was positive for anti-Dsg 1 (index value: 146; cut-off: 14) but negative for anti-Dsg 3. Based on these results, PF was diagnosed. ELISA for anti-Dsg 1 and Dsg 3 was retrospectively examined for the serum extracted in 2007, and results was negative. The patient refused to use systemic steroids. Complete remission has not been achieved using topical corticosteroids. However, the clinical severity of PF has been stable, and the index value of anti-Dsg1 Ab by ELISA has been around 40.

## DISCUSSION

To date, there are only 6 cases of ABD including our case reported in the English literature (3–7) (Table S1<sup>1</sup>).

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**Fig. 1.** (A, B) Clinical presentation of dermatomyositis at initial appearance in July 2007. (A) Pruritic malar erythema on the face, including the medial canthi of the eyes and alar part of the nose. (B) Gottron's papules on the dorsum of the right hand. (C) Clinical presentation of pemphigus foliaceus (PF) in June 2010. Mild erythema and erosions were observed on the back. (D) Histopathological findings of erythematous lesion of PF (H&E, original magnification  $\times 200$ ). Acantholysis and superficial split in the granular layer were observed.

There were 3 cases of bullous pemphigoid, 1 pemphigus vulgaris, and 2 PF. Five cases showed muscle weakness, and only our case was diagnosed with CADM. The interval between the onset of DM and ABD was 2 weeks to 4 years. All cases with skin eruptions showed Gottron's papules and facial erythema. The facial eruption was not described as a heliotrope rash; however, details such as the distribution were not reported in most cases. Facial erythema was observed in 67% of DM cases (8). Therefore, facial erythema excluding heliotrope rash may have an association with the induction of ABD Abs.

While the Ab of DM was unknown in 5 of the reported cases, anti-NXP2 Ab was identified in our case. Anti-NXP2 Ab, formerly known as anti-MJ Ab, is one of the myositis-specific Abs and can be found in juvenile DM patients with cutaneous calcinosis. In contrast, only limited cases with anti-NXP2 Ab have been reported in adult DM patients. Recently, it was reported that anti-NXP2 Ab was found in 1.6% of adult DM patients and associated with malignancy (2). In our case, malignancy and calcinosis have not been detected for 6 years.

We speculate that the coexistence of DM and ABD is not coincidental. It has been suggested that the Abs of ABD are caused by epidermal damage resulting from DM (5). In our case, anti-NXP-2 Ab was detected. NXP-2, also known as MORC3 (microorchidia family CW-type zinc finger 3), which is one of the MORC-family nuclear proteins, has specific RNA binding function and plays important roles in various nuclear functions, including RNA metabolism and maintenance of nuclear architecture. NXP-2 is localised in the nucleus, distributed to the nuclear matrix, and ubiquitously expressed (9). NXP-2 also regulates the activity of tumour suppressor protein, p53, and its localisation into promyelocytic leukaemia-nuclear bodies (10). Although NXP-2 is reported to have a possible role in SUMO (small ubiquitin-like modifier)-mediated transcriptional repression and the SUMO pathway may play a potential role in the pathogenic mechanisms of DM (11), the exact pathogenic role of NXP-2 in DM is still unclear. One possibility concerning the association between anti-NXP-2 Ab and anti-Dsg Ab is that DM and pemphigus can be linked to malignancy because anti-NXP-2 Ab is reported to be associated with malignancy (2). However, the clinical presentation of our patient does not preempt paraneoplastic pemphigus, and malignancy has not been found. Moreover, ABD followed the onset of DM in all reported cases, and there was only one case of ABD associated with polymyositis, another idiopathic inflammatory myopathy (12) (Table S1<sup>1</sup>). Based on these results, the occurrence of anti-Dsg Ab seems to be more likely associated with constant epidermal damage in DM than with anti-NXP-2 Ab.

Regarding the Abs following epidermal damage, it has been reported that circulating Abs for the basement membrane zone were detected by immunoblot in 24%

of sera from graft-versus-host disease (GVHD) patients after haematopoietic cell transplantation (HCT) (13). However, the types of ABD after GVHD and DM do not appear to be similar. Although almost all reported cases of ABD after HCT were subepidermal blistering diseases (14), half of the cases of ABD after DM were pemphigus (Table S1<sup>1</sup>). Further investigations including those on DM Abs are needed to clarify the association between ABD and DM.

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