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Plectin deficient epidermolysis bullosa simplex with 27-year-history of muscular dystrophy

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Summary

Background: Epidermolysis bullosa simplex associated with muscular dystrophy is caused by plectin deficiency.
Objective: To report clinical, immunohistochemical, ultrastructural and molecular features of a 52-year-old Japanese patient affected with this disease, whose muscular disease had been followed-up for 27 years.
Methods: We performed histopathological study, immunofluorescence, electron microscopic study and mutation detection analysis for plectin.
Results: The patient developed blisters and erosions followed by nail deformity on the traumatized regions from birth. The skin lesions were continuously developed to date. The histopathological study showed subepidermal blister. Electron microscopic study showed blister formation inside the basal cells at the level just above the attachment plaque of hemidesmosome. Immunofluorescence showed complete loss of staining to plectin. The mutation analysis using protein truncation test and DNA sequencing revealed a C-to-T transition at nucleotide position 7006 of the plectin cDNA sequence, which lead a novel homozygous nonsense mutation (R2319X).
Conclusion: From the above results, the diagnosis of epidermolysis bullosa simplex associated with muscular dystrophy was made. Slight muscular dystrophy was noticed at the age of 25 years. The muscular dystrophy gradually progressed and she could not walk at the age of 46 years. However, she can still breathe and swallow by herself. This

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is the patient of this disease with the longest follow-up, and may indicate the slow progress of muscular condition of this disease.

1. Introduction

Epidermolysis bullosa (EB) is a group of hereditary blistering disease that is divided into three major categories on the basis of the level of tissue separation within the dermal—epidermal junction [1,2]. Underlying molecular defect in each category has recently been disclosed. EB simplex is a genetic disorder characterized by blister formation within the basal cells [3]. The major subtypes of EB simplex have been shown to associate with mutations in basal keratinocyte-specific keratin genes, K5 and K14 [4,5]. In the lethal type of junctional EB, tissue separation occurs within the lamina lucida of the basement membrane zone, and mutations in the genes (LAMA3, LAMB3 and LAMC2) encoding the subunit polypeptides of laminin 5 have been disclosed [6]. All types of dystrophic EB show mutations in COL7A1 gene encoding type VII collagen [7].

In addition, new group caused by defects in hemidesmosomes has recently been classified as hemidesmosomal type, which included EB with muscular dystrophy, non-lethal junctional EB due to BP180 defect and EB with pyloric atresia due to defect of either α6 or β4 integrin [2].

EB associated with muscular dystrophy (EB—MD) is a rare subtype characterized by generalized blisters associated with muscle involvement [8—11]. Most cases showed late onset muscular disease, although some cases showed relatively early onset. Several cases have been found to show defective expression of plectin, and various mutations in the plectin gene, PLEC1, have been reported [12—32].

Plectin, a high molecular weight protein, is an intermediate filament binding protein found in a variety of cell types [30,31]. In the skeletal muscle, plectin is found in the sarcolemma and in the Z-line structures [33]. In the skin, it seems to localize in both the desmosomes and the hemidesmosomes where it associates with keratin intermediate filaments [34]. At the basement membrane zone, specific monoclonal antibody against plectin/HD1 has shown that plectin localizes to inner part of the hemidesmosomal plaques, close to the region where the 230 kDa bullous pemphigoid antigen localizes [35].

In this report, we described a 52-year-old female Japanese case with this disease, whose muscular disease was followed-up for 27 years.

2. Materials and methods

2.1. Report of a case

On October 2000, a 52-year-old Japanese female was referred to us for the diagnosis and treatment of generalized blistering and erosive skin lesions. She showed skin lesions (blisters and erosions) on the entire body from birth. She noticed nail deformity and she also lost most of her teeth in early age. No hair abnormality was seen. Although blister formation continued, muscle symptom had never been found, until muscle weakness on the arms was first noted at the age of 25 years. Muscle weakness gradually progressed, but she could perform routine activities of daily life. However, she could not walk at age of 46 years, due to widespread muscular atrophy. She is now on bed and is confined to a wheelchair.

She had surgery for pyelonephritis at the age of 17 years. She also had surgery for possible breast cancer at the age of 29 years.

She was the youngest sister among 8 siblings (4 males and 4 females) (Fig. 1). Two siblings (3rd brother and 2nd sister) were reported to die at an age of about 2 years by blistering skin disease. Her father was dead by brain disease, and her 92-year-old mother was alive. Precise pedigree for the parents could not be obtained and therefore, consanguinity was not clear.

On the physical examinations, she showed multiple blisters, erosions and pigmentation on the whole body, particularly on the traumatizing areas, such as the limbs and neck (Fig. 2a—c). Slight scar formation was also seen in some areas. Her nails are also severely damaged (Fig. 2c). No oral mucosal lesion was seen, and she did not show hoarse voice. How-

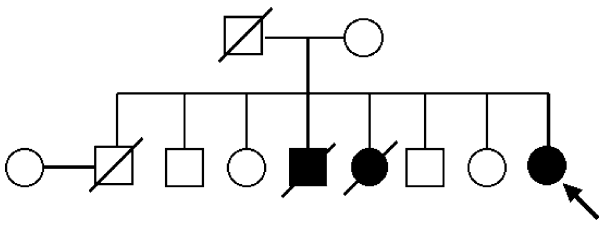

Fig. 1 Family pedigree. The presented case is indicated by an arrow. Two elder siblings were suspected to die due to the same skin disease.