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CASE REPORT

A Novel Frameshift Mutation of Galactosidase-alpha in Fabry Disease Restricted to Dermatologic Manifestations

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A 28-year-old Asian male was referred for dermatologic evaluation of diffuse bluish-red maculopapules in the lower trunk and genital regions. There was no family history, and with the exception of dispersed skin lesions and hypohidrosis, no other complaints or symptoms were present. Histological evaluation of the skin lesions revealed angiokeratomas. When this combination of clinical and histological findings is observed, Fabry disease is suspected. Biochemical examination performed for definitive diagnosis did not show any activity of the α-galactosidase A enzyme. Through identification of a c.182_183ins(GA) mutation of the GLA gene, Fabry disease was diagnosed. However, there was no particular abnormal finding with regard to the evaluation of non-cutaneous manifestations, a symptom that can occur in the progress of this disease. We reported a case of Fabry disease, restricted to the dermatologic presentation, involving a novel frameshift mutation in the GLA gene. **(Ann Dermatol 25(1) 95～98, 2013)**

-Keywords-
alpha-galactosidase A, Mutation, Skin manifestation

INTRODUCTION

Fabry disease is an inherited deficiency of the lysosomal hydrolase alpha-galactosidase A (aGalA). Deficiency of aGalA leads to a systemic accumulation of globotriaosylceramide (GL-3) and related glycosphingolipids in the plasma and tissue lysosomes, causing multisystem disease[1].

We describe a 28-year-old man who presented with the classic skin symptoms of angiokeratomas and hypohidrosis without other manifestations of Fabry disease. The diagnosis of Fabry disease was made clinically and confirmed by demonstration of deficient leukocyte α-Gal A activity and genomic mutations in the GLA gene. Here, we report a case of Fabry disease, restricted to the dermatologic presentation, involving a novel frameshift mutation in the GLA gene.

CASE REPORT

A 28-year-old Asian male presented with a 4-year history of small, raised, reddish-purple maculopapules affecting his genital area and lower trunk. He was otherwise well, with no past medical history with the exception of hypohidrosis since childhood. There was no family history of kidney failure, heart disease, stroke, or other signs or symptoms of Fabry disease.

On examination, skin lesions tended to increase in number and size with age, and were clustered prominently and densely around the penis and scrotum (Fig. 1). Tiny macules were peppered over the patient's lower abdomen and back (Fig. 2).

Renal function panel, including glomerular infiltrate rate and urine microalbumin, were normal. Electrocardiogram and echography also showed normal cardiac chamber

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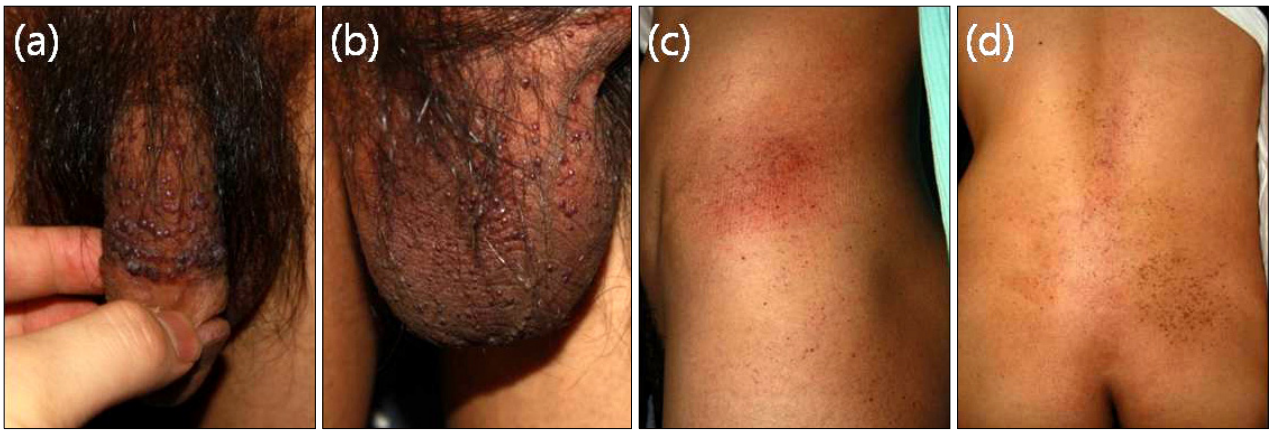

Fig. 1. (A, B) Numerous small, raised, reddish-purple maculopapules affecting the genital area and (C, D) lower trunk. These were more prominent and dense around the penis and scrotum, but tiny papules were peppered over the lower abdomen and back.

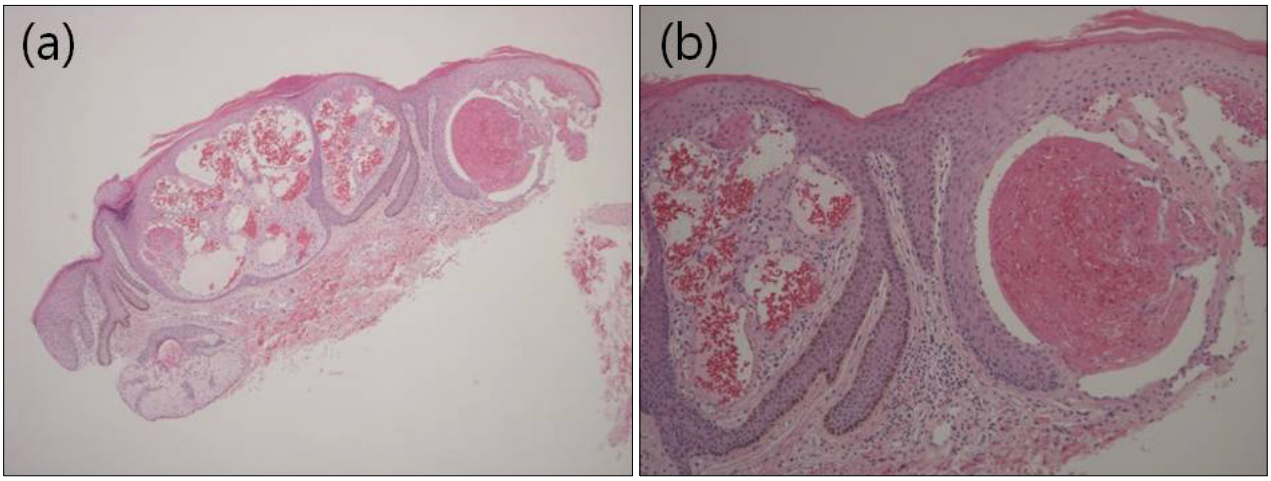

Fig. 2. Photomicrograph showing hyperkeratosis in the epidermis and dilated capillary vessels in the upper dermis (A: H&E, ×40; B: H&E, ×100).

size and wall thickness. In addition, no abnormalities were found on brain magnetic resonance imaging or neurologic examination. There were no aneurysmal dilatations of the conjunctival vessels or diffuse corneal opacities (i.e., corneal verticillata) on ophthalmologic investigation.

Histologic examination of skin biopsies from the left side of the abdomen and penile shaft revealed a moderate hyperkeratosis with dilated blood vessels filled with erythrocytes in the epidermis (Fig. 3). In the upper dermis, enormously dilated vessels were present, some surrounded by epithelial sprouts. A moderate lymphohistiocytic infiltrate was observed. These findings were consistent with a diagnosis of angiokeratoma.

The clinical symptoms and histological findings described above suggested the possibility of Fabry disease. The appropriate biochemical examination required to confirm the diagnosis was made through demonstration of deficient α-galactosidase A activity and identification of a pathogenic mutation of GLA. With the addition of N-acetylgalactosamine, the activity of α-galactosidase B was eliminated. Enzyme activity of the patient, as determined by fluorescence of 4-methylumbelliferryl, confirmed a GLA enzyme deficiency with an average of 0.00 nmole/hr/mg. Furthermore, in order to determine whether GLA was mutated, polymerase chain reaction sequencing was done with the use of the DNA separated from peripheral blood. Analysis of the DNA sequence for the exon and exon-intron boundaries of seven GLA genes revealed a c.182_183ins(GA) (pAsp61GlufsX32) frameshift mutation at exon1.

Due to the patient's personal reasons, genetic counseling and evaluation of family members were not performed, but the family history gave no suspicion of Fabry disease.

Result: c.182_183ins(GA) (p.Asp61GlufsX32) and no activity of α-Gal

▪ α-Gal enzyme activity by fluorescence of 4-MU

	1st assay		2nd assay	
	Blank	Activity	Blank	Activity
Fluorescence	143.99	151.25	143.99	136.72
Used protein (mg)	0.015			
1 nmole 4-MU fluorescence	~6,000			
Protein activity (nmoles/hr/mg)	0.00			

Normal ranges[1]: leukocytes: 32.6~88.2 (nmoles/hr/mg) [n=33]

▪ Partial seq. of *GLA* gene

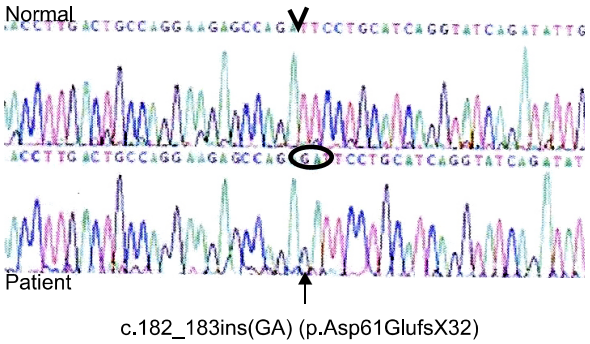

Fig. 3. No activity of α-galactosidase B was observed. A c.182_183ins(GA) (pAsp61GlufsX32) mutation was identified at exon1.

Enzyme replacement therapy (ERT) is currently being administered, and symptoms are being managed through constant observation of progress.

DISCUSSION

Fabry disease, an X-linked lysosomal storage disorder caused by the deficiency of α-galactosidase A, is associated with dysfunction of many cell types and results in a systemic vasculopathy[2]. The mutations responsible for Fabry disease are located at Xq22; over 500 different GLA mutations have now been identified. Most mutations are point mutations (83.4%), including missense (50.0%), nonsense (29.2%), and splicing (4.2%) mutations, although a few deletion or insertion mutations have been found to cause frame-shifts (16.6%)[3].

In the past, most GLA mutations were considered as private, making genotype-phenotype correlation difficult[4]. However, according to recent studies, a correlation between the mutation of particular exon codes, such as exons 3 and 7, and the most severe disease phenotypes is being reported. There appears to be a correlation between clinical phenotypes and three-dimensional structural changes in protein cores or functionally important regions by various mutations[5,6].

The disease manifestations often start in childhood or adolescence, and include pain and burning sensations in the hands or feet that worsen with exercise or hot weather. Additional symptoms may include typical skin lesions (angiokeratomas), decreased sweating, cloudiness of the cornea, abdominal discomfort, and back pain. With advancing age, progressive lysosomal GL-3 accumulation in the vascular endothelium leads to chronic renal disease, vascular disease of the heart and brain, and premature demise in the fourth and fifth decades of life[7].

Recently, later-onset variants with residual α-Gal A activity that lack vascular endothelial involvement and classic symptoms (i.e., angiokeratomas, acroparesthesias, hypohidrosis, and ocular abnormalities) have been reported. These variants typically present with renal and/or cardiac disease in the sixth decade of life or later[8,9].

A presumed diagnosis of Fabry disease in males with classic or variant phenotypes can be reached by the demonstration of markedly deficient α-Gal A activity in plasma, isolated leukocytes, and/or cultured cells[10]. However, females often have mildly reduced or normal enzyme activity due to random X-chromosome inactivation. Therefore, the finding of a mutated α-galactosidase A gene (GLA) is critical for confirmation of Fabry disease in females[11]. In our patient, no enzyme activity existed, and c.182_183ins(GA) mutation was observed; therefore, Fabry disease was diagnosed by a frameshift mutation. Although our patient was introduced in a previous report[3], there were no descriptions on the patient's clinical appearance.

Our patient had angiokeratoma and hypohydrosis, but no acroparesthesia or ocular manifestations. Other tests revealed no abnormalities involving the neural system, kidney, or heart. Rarely, Fabry disease shows only typical skin lesions with no clear family history and requires early diagnosis to prevent organ failure. Therefore, the dermatologist who offers treatment for the first time plays an important role in the initial diagnosis and the prognosis. If any of the related symptoms are present in young male patients, Fabry disease must be considered and early therapeutic intervention is necessary to retard the life-thre-

atening progression of the disease.

In the past, limited palliative or non-specific treatment was preferred. However, since its introduction in Europe in 2001, ERT is being widely used as the most effective treatment method in the reduction of various complications and improvement of life quality through specific treatments that clears the accumulated GL-3[2].

In summary, we reported a hemizygous male patient with Fabry disease restricted to the dermatologic presentation, and involving angiokeratoma and hypohidrosis without other manifestations of Fabry disease. This is a rare clinical phenotype of Fabry disease involving a frameshift mutation in the GLA gene.

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