

CASE REPORT

A case of Cowden syndrome with a novel mutation in the *PTEN* gene

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Abstract : Cowden syndrome (CS) is an autosomal dominant inherited disorder characterized by macrocephaly and multiple hamartomas. The responsible gene is *PTEN* (phosphate and tensin homolog detected on chromosome 10), which negatively regulates cell proliferation and survival. We herein present a 46-year-old woman with the typical clinical features of CS. A DNA sequencing analysis of the coding regions and flanking introns of the *PTEN* gene revealed a novel heterozygous mutation (c.403A > G, p.Ile135Val) in exon 5 that had not been previously reported in CS. *J. Med. Invest.* 67:200-201, February, 2020

Keywords : Cowden syndrome, *PTEN* gene, novel missense mutation

INTRODUCTION

In 1963, Lloyd and Dennis reported Cowden syndrome (CS), also called Cowden disease, as a possible inherited symptom complex, including an adenoid face, trichilemmomas on the face, papillomatosis of the oral mucosa, and multiple thyroid adenomas (1). Diagnostic criteria for CS were initially established in 1996 and then revised in 2013 based on clinical experience and a large number of case reports (2). Besides multiple hamartomas, CS is recognized as a cancer-prone syndrome. A linkage analysis showed that a single locus within chromosome 10q22-23 was responsible for CS (3). In 1997, with a focus on somatic mutations in cancer cell lines, Li *et al.* isolated the *PTEN* gene as a candidate tumor suppressor gene by mapping homozygous deletions within 10q23 (4). After the identification of the *PTEN* gene, *PTEN* was proposed as the susceptibility gene for CS (5). Many *PTEN* mutations have since been detected in CS among unrelated patients or families (6). The sites of heterozygous mutations are distributed along whole *PTEN* exons, except for exon 9 (6). The detection of a germline mutation in a patient currently provides molecular confirmation for the diagnosis of CS.

CASE REPORT

A 46-year-old Chinese woman presented at our hospital with an increasing number of acral keratoses. The woman had moved from Xi'an to Tokyo at the age of 43 years and underwent a medical examination at another hospital in Tokyo that revealed multiple adenomas in the thyroid gland, cysts in both breasts, five benign gastrointestinal polyps, and an endometrial adenoma. At the age of 45 years, asymptomatic verruciform papules appeared on the upper lips. Two months later, she noted smooth skin-colored papules on her palms and soles. When she presented to our hospital, ten trichilemmoma-like papules were present

on her face and multiple oral papillomas on the gingivae (Fig. 1). There were also several small keratotic papules on palmoplantar surfaces (Fig. 2). The histopathological findings of acral skin were hyperkeratosis, hypergranulosis, and acanthosis in the epidermis without inflammation and/or vasodilatation in the upper dermis. There were no signs of viral infection. Her head circumference was 61.5 cm, which was larger than the 97th percentile. No malignant tumors were detected in any organs. The *PTEN* Cleveland Clinic adult score (7) was 48, corresponding to a mutation probability of greater than 99%. Informed consent was obtained from the patient to analyze genomic DNA. A direct DNA sequencing analysis showed a haplotype c.403A > G (adenine to guanine) mutation in exon 5 of the *PTEN* gene (Fig. 3). The mutation resulted in a p.I135V (isoleucine to valine) substitution. Her family history was unclear because her father had already passed away. Based on the findings of a gene analysis performed in China, her clinically unaffected mother and half-sister from a different father did not carry the mutation. Since her diagnosis, the patient has undergone annual medical check-ups because the altered *PTEN* protein increases the risk of developing malignancy.



Fig 1. Cobble-like lesion on the gingiva

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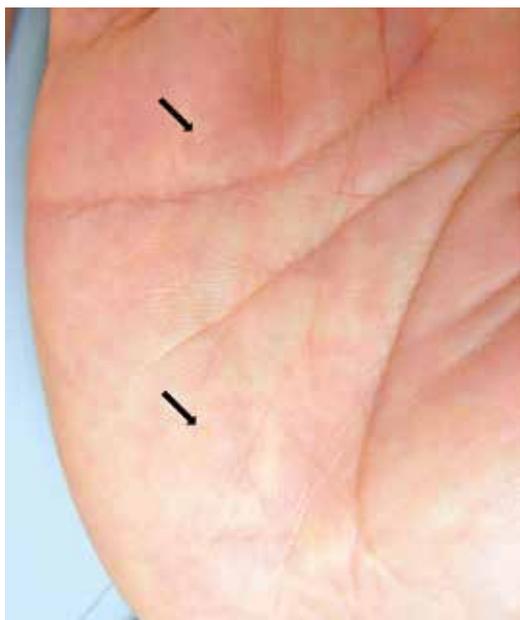


Fig 2. Keratotic papules on the right palm (arrows)

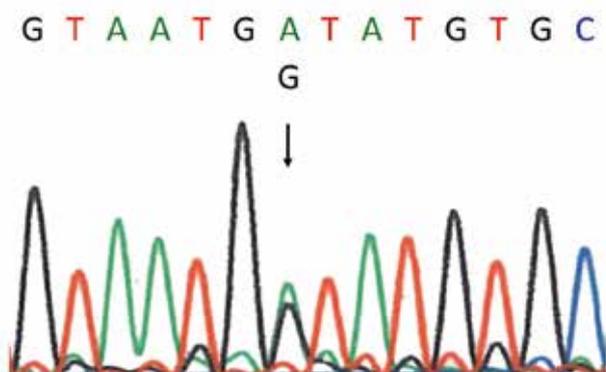


Fig 3. A direct sequencing analysis of genomic DNA revealed an A to G transition at nucleotide position 403 in exon 5 of the *PTEN* gene.

DISCUSSION

CS is one of the *PTEN* hamartoma tumor syndromes (PHTS) and is characterized by hamartomas in several organs (8). Characteristic features of CS are macrocephaly, facial trichilemmomas, acral keratosis, papillomatous papules, and thyroidal adenomas. Nodules and/or cysts in the thyroid gland may appear as the initial manifestation and are generally found one to two years prior to skin lesions. Papules on the skin and oral papillomas typically appear in the second to third decade of life. The present middle-aged case had fewer hamartomas in each organ than age-matched typical CS cases diagnosed in their twenties due to the late onset of the disease.

The patient had an I135V mutation in exon 5 of the *PTEN* gene. This mutation had not been previously reported in CS; however, a case of Bannayan-Riley-Ruvalcaba-syndrome, another phenotype of PHTS, had the same mutation (9). The mechanisms

by which an identical mutation produces distinct phenotypic features have not yet been elucidated. A mutation in the *PTEN* gene is observed in 81% of CS cases, and 43% of CS patients harbor each mutation in exon 5 (10). Exon 5 encodes a core motif of phosphatidylinositol 3'-phosphatase, a key enzyme that negatively regulates the PI-3 kinase pathway. Four missense mutations (G129E, R130Q, R130L, and C136Y) and two nonsense mutations (R130X and L139X) have been identified near codon 135 in CS individuals (6). The findings of an *in silico* analysis using PolyPhen-2 software (prediction of functional effects of human nsSNPs) suggested that this I135V mutation was damaging with a score of 0.993 (11). Another analysis with fathmm software (Functional Analysis through Hidden Markov Models) indicated that the missense mutation damaged the function of the *PTEN* protein (12). The I135V mutation may cause the haplo-inactivation of the *PTEN* protein. Further *in vitro* investigations are required.

CONFLICT OF INTEREST

None declared.

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