Cowden syndrome (CS; OMIM #158350) is a rare autosomal dominant disorder characterized by multiple hamartomas of ectodermal, mesodermal and endodermal origins. CS patients have a high risk of developing breast, thyroid and endometrial cancers (1). Typical mucocutaneous symptoms include facial trichilemmomas (hamartomas of the infundibulum of the hair follicle), acral keratoses and mucocutaneous papules. Other mucocutaneous lesions include dermal fibromas, scrotal tongue and skin tags (2). Additional disease features may include adult-onset Lhermitte-Dulclos disease (LDD) (a dysplastic gangliocytoma of the cerebellum), macrocephaly, mental retardation and structural malformations in the genitourinary system (3). This list has recently been revised (4).

PTEN is a tumor suppressor gene located on chromosome 10q23.3. It encodes a phosphatase that influences the cell cycle, causing G1 arrest and apoptosis (5). PTEN hamartoma tumor syndromes (PHTS) are a group of disorders characterized by PTEN mutations and hamartomas of multiple organ systems. They include CS, Bannayan-Riley-Ruvalcaba syndrome (BRRS; OMIM #153480), Proteus syndrome, and Proteus-like syndrome (6). Some 85% of CS patients carry germline loss-of-function mutations in the PTEN gene. Among PHTS, it has been reported that BRRS and CS share clinical characteristics and represent a single entity. However, BRRS can be clinically differentiated from CS by hamartous polyposis, macrocephaly, lipomatosis, hemangioma and a speckled penis.

A Novel PTEN Mutation in a Korean Patient with Cowden Syndrome and Vascular Anomalies

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DISCUSSION

According to the results of mRNA sequencing, the novel germline deletion mutation causes transcriptional skipping of exon 3. The novel germline mutation identified in this study is predicted to cause single amino acid substitution

Fig. 1. Multiple rice grain-sized papules were present on the face.
whether or not the modified PTEN molecule was synthesized in vivo.

PTEN contains two key domains: the N-terminal domain and the C-terminal domain. Most PTEN mutations occur within the N-terminal phosphatase domain (amino acids 1-185). Analysis of the structure of PTEN revealed that its phosphatase domain, although similar to those of other phosphatases, has a slightly larger active site. This larger active site is accessible to phospholipid substrates, a unique feature of PTEN (7). It is also a mutational hot spot. This is especially true of exon 5, which accounts for 20% of the entire coding sequence and encodes the catalytic core. Exon 5 carries about 40% of the germline mutations in this gene. Approximately two-thirds of all mutations are found in exons 5, 7 and 8. Mutations in exon 3 have rarely been reported (8).

It has been demonstrated that genetic background and modifier genes more strongly influence the onset and spectrum of tumor formation than the specific PTEN mutation present (9).

Facial trichilemmomas, a hallmark of CS, were not detected, despite multiple skin biopsies of the facial papules being analyzed. Brownstein et al. (10) reported that biopsies of multiple facial skin lesions were necessary in order to detect evidence of trichilemmomas. It has been reported that punctate palmoplantar keratoses in childhood without other mucocutaneous lesions may be a clue for the early diagnosis of PHTS (11). Our patient’s symptoms – multiple facial papules, palmar keratoses, papillary thyroid cancer, thyroid adenomatous hyperplasias and a germline PTEN mutation – strongly suggest that the PTEN hamartoma tumor syndrome she is suffering from is CS.

Our patient exhibited two vascular anomalies. One was a cutaneous hemangioma, and the other a cervical paraspinal AVM. Recently, Tan et al. (12) described 26 patients with vascular anomalies and PTEN mutations. They identified AVMs in 54% of the patients with PTEN mutations. This high frequency may be explained by the make-up of the study population, which included individuals who had been treated at a vascular anomalies center. None suffered from hemangiomas or other pure vascular tumors, and paraspinal AVM was found in only two cases.

There is growing evidence that PTEN has an anti-angiogenic effect (13) and it inhibits endothelial tube formation induced by vascular endothelial growth factor (VEGF) (14). Furthermore, loss of the PTEN gene results in subsequent VEGF expression (15).

Our patient wanted her daughter to undergo genetic testing, although she did not have any features of CS, including mucocutaneous lesions and macrocephaly. Examination of the daughter revealed her to be carrying the same germline PTEN mutation, and she was recommended for surveillance according to NCCN criteria (2).

The authors declare no conflict of interest.

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(R55S) and deletion of amino acids 56-70 in PTEN’s N-terminal phosphatase domain. We were unable to confirm whether or not the modified PTEN molecule was synthesized in vivo.

Fig. 2. Histopathological features. (a) Follicular keratotic plugging of a facial papule. (b) Acanthosis with hypergranulosis and marked orthokeratosis in a palmar keratosis. (a, b) H&E, original magnification ×100.

Fig. 3. A four-nucleotide deletion (c.209+4_7delAGTA) in exon 3 of the PTEN gene. Arrow, deleted nucleotides; W, wild-type allele; M, mutated allele.

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