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Letter to the editor

Multiple keratotic papules and plaques on the trunk in Cowden's disease with MALT lymphoma

Sayaka Mizuno[1], Takuya Takeichi[1], Junichi Sato[2], Masanao Nakamura[2], Hidemi Goto[2], Kazumitsu Sugiura[3] and Masashi Akiyama[1]

[1]Department of Dermatology, [2]Department of Gastroenterology and Hepatology, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan
[3]Department of Dermatology, Fujita Health University School of Medicine, Toyoake, Japan

Correspondence:
Masashi Akiyama, MD, PhD
Tel: 81-52-744-2314, Fax: 81-52-744-2318
E-mail: makiyama@med.nagoya-u.ac.jp

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Cowden's disease (CD) is a multisystem disease complex with autosomal dominant inheritance.[1] Germline mutations in *PTEN*, a putative tumor suppressor gene, have been identified in two autosomal dominant inherited hamartoma syndromes, CD and Bannayan-Riley-Ruvalcaba syndrome (BRRS). [2,3] The most common features of CD are mucocutaneous findings of facial papules, mucosal lesions, acral keratosis and palmoplantar keratosis. CD has high risk of breast, thyroid and endometrial carcinomas. Gastrointestinal polyposis was found less frequently. Here, we describe the atypical spreading of multiple epidermal hyperkeratotic papules and plaques to the trunk in a case of CD complicated with gastric extranodal marginal-zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma).

The patient is a 60-year-old Japanese woman with no family history who has had multiple brown papules and plaques scattered over the face, neck, forearms, lower leg and trunk for 3 years (Fig. 1a and b). Warty, hemispherical papules were present on the tongue (Fig. 1c). She had no palmoplantar keratoderma. A skin biopsy from a keratotic papule on the left thigh revealed mild papillomatosis of the epidermis accompanied by hyperkeratosis (Fig. 1d). Her history included endometrial carcinoma at 52 years of age, mammary carcinoma at 56 years of age, thyroid tumor at 59 years of age, and nonalcoholic fatty liver, pancytopenia due to liver cirrhosis, diabetes mellitus and hypertension. Upper gastrointestinal endoscopy revealed multiple whitish flatly elevated lesions scattered on the entire esophagus and multiple polyps on the whole stomach (Fig. 1e). When she was 43 years old, biopsies from several polyps revealed MALT lymphoma. The MALT lymphoma was treated with *Helicobacter pylori* eradication triple therapy (a proton pump inhibitor, amoxicillin and clarithromycin).

Ethical approval was obtained, and all research was performed in accordance with the *Declaration of Helsinki* principles. Following informed consent, genomic DNA

from the affected individual was used for standard PCR and Sanger sequencing of the coding exons and flanking introns of *PTEN*. The Sanger sequencing identified the previously reported heterozygous mutation c.70G>C (p.Asp24His) of *PTEN*. The mutation p.Asp24His identified in *PTEN* here has been reported previously as a pathogenic substitution in an individual with CD.[4] Two mutations at the corresponding asparagine residue Asp24 within the *PTEN*, p.Asp24Gly in CD and p.Asp24Tyr in BRRS, have been reported previously.[5] Although reliable genotype/phenotype correlations in *PTEN* have not been clarified,[4] the substituted amino acids (His, Gly or Tyr) for the corresponding asparagine may determine whether the phenotype is CD or BRRS.

Most cases of CD have keratotic papules limited to the extremities. As far as we know, there are no reported CD cases showing many keratotic papules and plaques distributed not only on the extremities, but also over the entire trunk. Additionally, there are no reports of CD cases with MALT lymphoma, although CD is known as a syndrome with a high risk of multiple tumors. PI3K-Akt signal pathway activated by the *PTEN* mutation might be involved in the pathogenesis of MALT lymphoma. Our findings suggest the importance of checking the histology of mucosal lesions in the gastrointestinal tract carefully in CD patients.

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References

1. Salem OS, Steck WD. Cowden's disease (multiple hamartoma and neoplasia syndrome). A case report and review of the English literature. *J Am Acad Dermatol* 1983; **8**:686-696.

2. Liaw D, Marsh DJ, Li J, et al. Germline mutations of the PTEN gene in Cowden disease, an inherited breast and thyroid cancer syndrome. *Nat Genet* 1997; **16**:64-67.

3. Marsh DJ, Dahia PL, Zheng Z, et al. Germline mutations in PTEN are present in Bannayan-Zonana syndrome. *Nat Genet* 1997; **16**:333-334.

4. Tan MH, Mester J, Peterson C, et al. A clinical scoring system for selection of patients for PTEN mutation testing is proposed on the basis of a prospective study of 3042 probands. *Am J Hum Genet* 2011; **88**:42-56.

5. Tok Celebi J, Chen FF, Zhang H, et al. Identification of PTEN mutations in five families with Bannayan-Zonana syndrome. *Exp Dermatol* 1999; **8**:134-139.

Figure legends

Figure 1. The clinical features of the patient include multiple keratotic papules and plaques, and multiple gastric polyps from MALT lymphoma.

(a, b) Small brown keratotic papules and plaques diffusely distribute on the trunk. (c) Multiple reddish papules with a hemispherical appearance on the tongue. (d) A biopsy specimen from a keratotic papule shows mild papillomatosis of the epidermis, accompanied by hyperkeratosis. Scale bar: 100μm (e) An endoscopic view showing multiple polyps on the stomach wall.