



CASE REPORT

Cowden Disease: Case Report and Review of the Literature

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Cowden's disease is a rare autosomal dominant, multiple hamartoma syndrome with characteristic mucocutaneous lesions. It is associated with abnormalities of the breast, thyroid, and gastrointestinal tract; and is characterized by multiple hamartomas in the gastrointestinal tract and mucocutaneous lesions such as trichilemmomas, oral papillomatosis, facial papules, and acral keratosis. A 21-year-old male patient presented with erythematous facial papules, oral mucosal papillomatosis, and punctate palmoplantar hyperkeratosis indicating a definite case of Cowden's disease. This disease derives from variable expression resulting from a mutation in the *PTEN* gene. Gastrointestinal endoscopy and colonoscopy revealed multiple hamartomas in the stomach and colon. On thyroid ultrasonography, several probable benign nodules were noted in the right thyroid gland. He had no pertinent family history and no other systemic findings. Further regular laboratory and image studies will be planned for our patient, as well as his family members. Sporadic Cowden's disease is rarely observed. Herein, we report a

case of Cowden's disease without known family history. Dermatologists should be aware of the possibility of Cowden syndrome based on its several dermatologic findings. (**Ann Dermatol 31(3) 325 ~ 330, 2019**)

-Keywords-

Hamartoma syndrome, multiple, PTEN phosphohydrolase, Skin neoplasm

INTRODUCTION

Cowden's disease is a rare autosomal dominant, multiple hamartoma syndrome¹ characterized by multiple hamartoma of all three embryonic origins. It carries a high risk of breast, thyroid, and other cancers² as well as benign hamartomatous overgrowth of tissues (skin, colon, thyroid, etc.)³. Several sporadic cases have also been reported. The common mucocutaneous findings include facial trichilemmomas, oral papillomas, and acral and palmoplantar keratosis⁴. The original report in 1963 by Lloyd and Dennis first named the syndrome after their patient Rachel Cowden⁵. Cowden's disease is the most common of the phosphatase and tensin homolog (PTEN) hamartomatous tumor syndromes, which includes other syndromes such as Bannayan-Railey-Ruvalcaba syndrome, Proteus syndrome, and Proteus-like syndrome^{6,7}.

This article presents a case of Cowden's disease with special emphasis on the clinical and pathologic features of the skin lesions on both hands and feet, and oral manifestations. We report this rare condition along with a brief review of the disease.

CASE REPORT

A 21-year-old male patient presented with diffuse hyper-

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keratotic lesions with 1 to 2 mm tiny punctations on both his hands and feet. The patient reported that the lesions had slightly increased in number over the last 10 years without symptoms. He also presented with multiple localized erythematous papules on his forehead that had occurred about two years prior. He first visited the department of internal medicine due to repeated melena and hematochezia for about a month. While he underwent several examinations due to these symptoms, he also vis-

ited the department of dermatology for his cutaneous symptoms. There was no history of any other systemic disease or trauma. No other family member had similar lesions. Only his sister had a history of thyroid cancer.

On physical examination, multiple mucocutaneous lesions were observed. Multiple punctate hyperkeratotic macules were observed on both palms and soles (Fig. 1A, B). The facial skin showed multiple skin-colored papules on his nose (Fig. 1C). On his tongue and oral mucosa, several

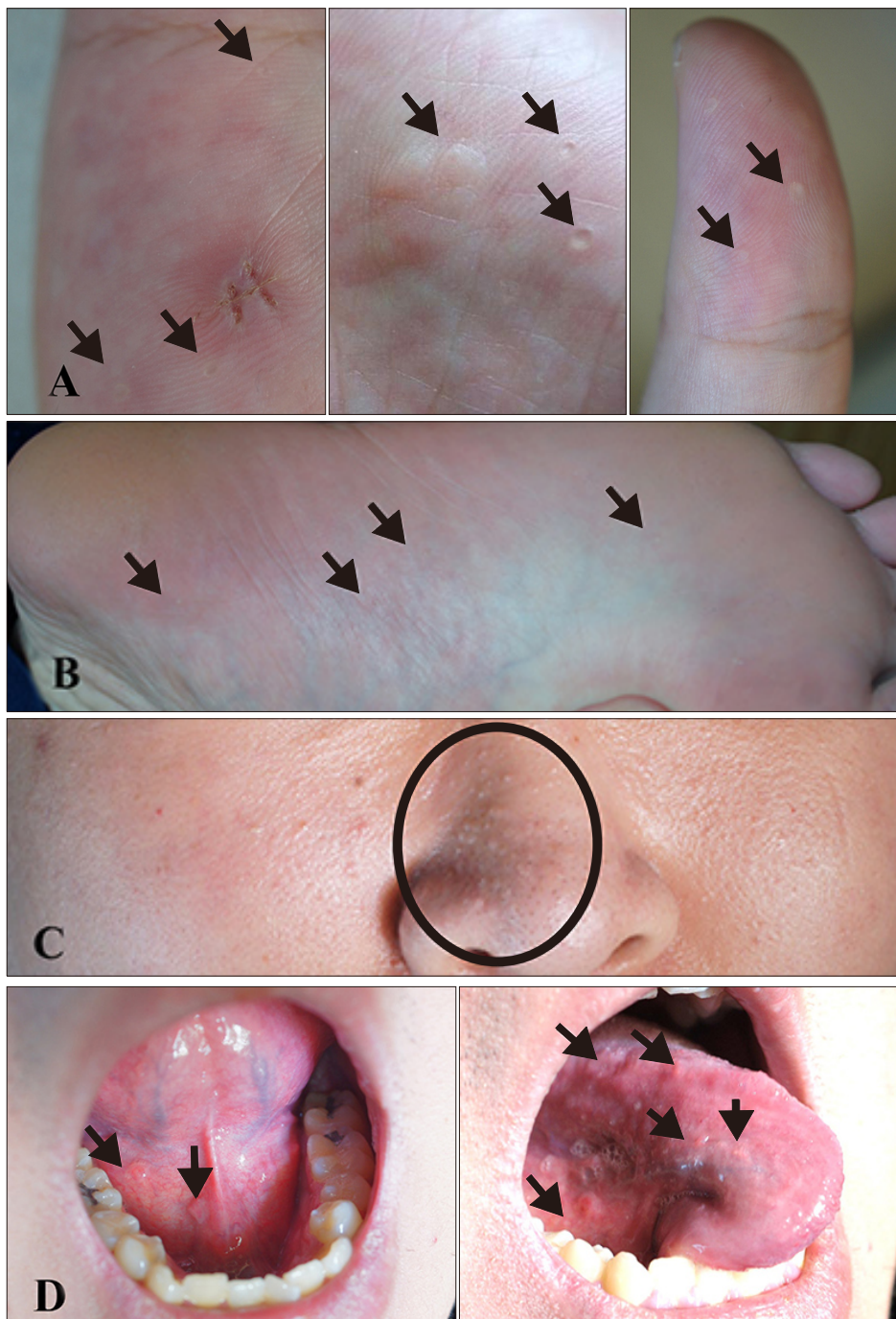


Fig. 1. Clinical images of the 21-year-old patient. Multiple punctate hyperkeratotic macules are localized on both (A) palms and both (B) soles (black arrows). Multiple skin-colored papules are observed on his (C) nose (black circle). On his (D) tongue and oral mucosa, several erythematous papules are found resembling cobblestones or fibroma-like polyps (black arrows).

erythematous papules were noted, with appearance slightly like cobblestones or fibroma-like polyps (Fig. 1D). We received the patient's consent form about publishing all photographic materials.

His esophagogastroduodenoscopy and colonofibroscope were abnormal, with numerous hamartomas papillomatosis over the entire lumen surfaces of stomach, duodenum, and esophagus (Fig. 2A). Biopsy of a gastric lesion and polypectomy showed histopathology of a gastric polyp with hyperplasty and an inflammatory polyp with prominent reactive lymphoid follicle (Fig. 2B). Colonoscopy

showed several small polyps (Fig. 2C). Histopathology of a colorectal polyp showed that it was inflammatory (Fig. 2D). In laboratory findings including a complete blood count, chemistry, and urinalysis, results were within normal range. The chest x-ray and electrocardiography showed no abnormal results.

Skin biopsy was performed on the palm and forehead. Biopsy of a punctate lesion on the palm revealed palmo-plantar keratosis with a large hyperkeratotic mound and thickened granular layer. Typical histologic backgrounds of palmo-plantar keratoderma, including marked hyper-

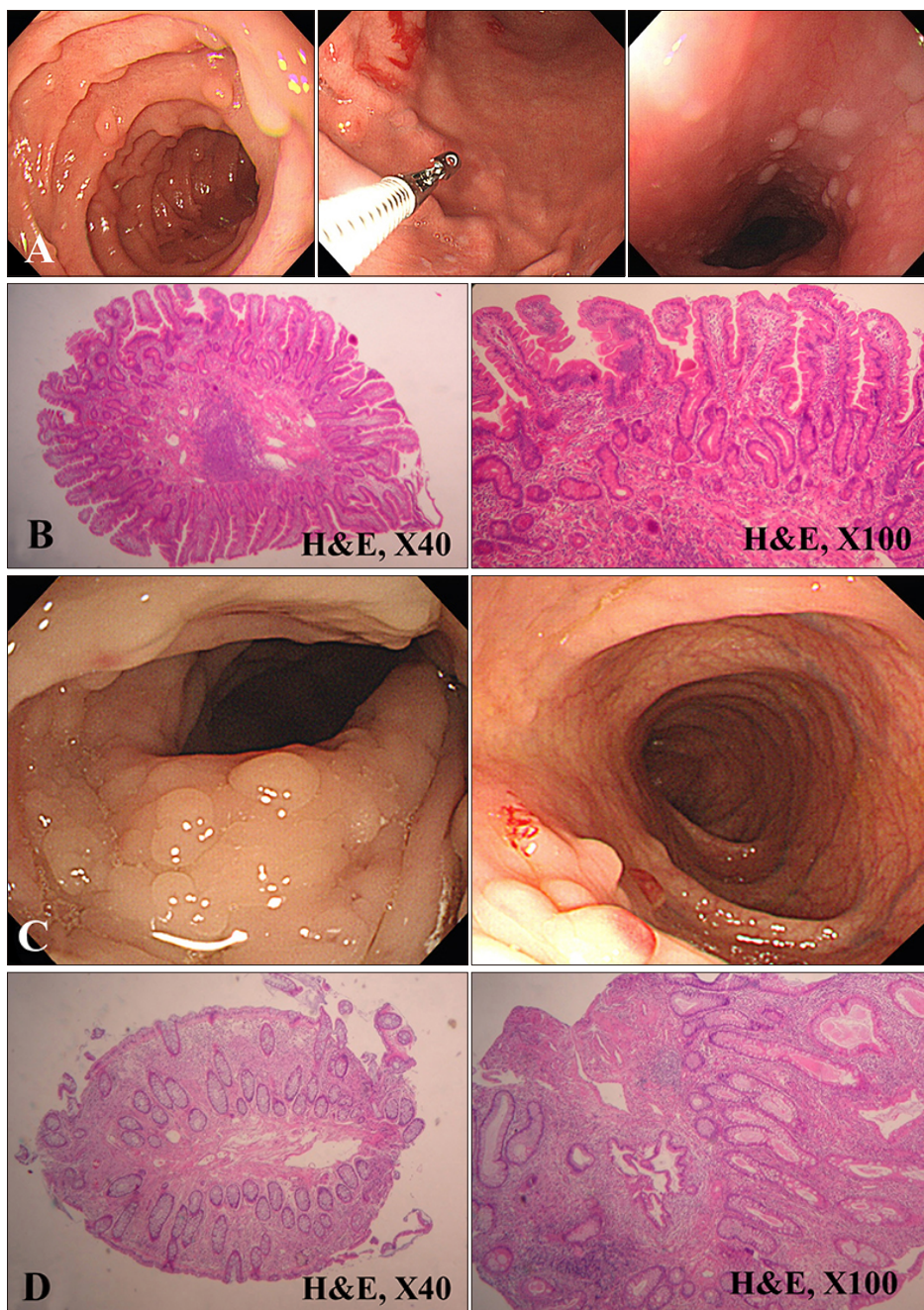


Fig. 2. (A) Endoscopic photograph showing multiple hamartomas papillomatosis in the duodenum and stomach, and esophageal keratosis like nodular lesions in the esophagus. (B) By biopsy of the gastric lesion and polypectomy, histopathology of a gastric polyp reveals a hyperplastic and inflammatory polyp with prominent reactive lymphoid follicle (H&E; $\times 40$, $\times 100$). (C) Colonoscopy shows several small polyps. (D) Histopathology of a colorectal polyp shows it to be inflammatory (H&E; $\times 40$, $\times 100$).

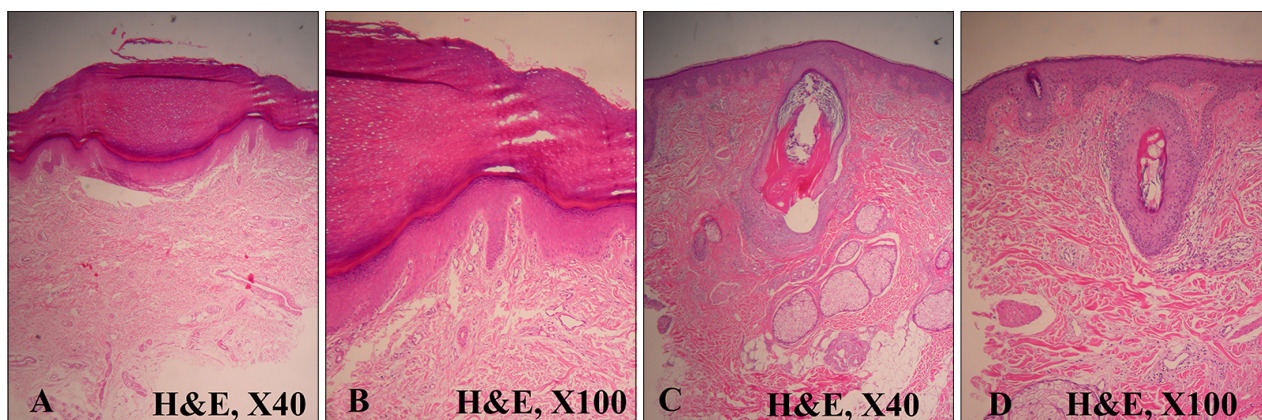


Fig. 3. (A) Hematoxylin and eosin (H&E) stained specimen from palm shows a large hyperkeratotic mount with thickened granular layer. Typical histologic backgrounds of palmoplantar keratosis, including marked hyperkeratosis and epidermal proliferation, are noted (H&E, $\times 40$). (B) Epidermal hyperplasia with hypergranulosis, a thin layer of parakeratosis, and overlying orthokeratosis can be observed. Slightly dilated blood vessels in the papillary dermis and a sparse infiltrate of lymphocytes are noted (H&E, $\times 100$). (C, D) A specimen from forehead shows plugging of the hair follicle by keratin with typical histologic backgrounds of acne including perifollicular lymphocyte infiltration (H&E; C: $\times 40$, D: $\times 100$).

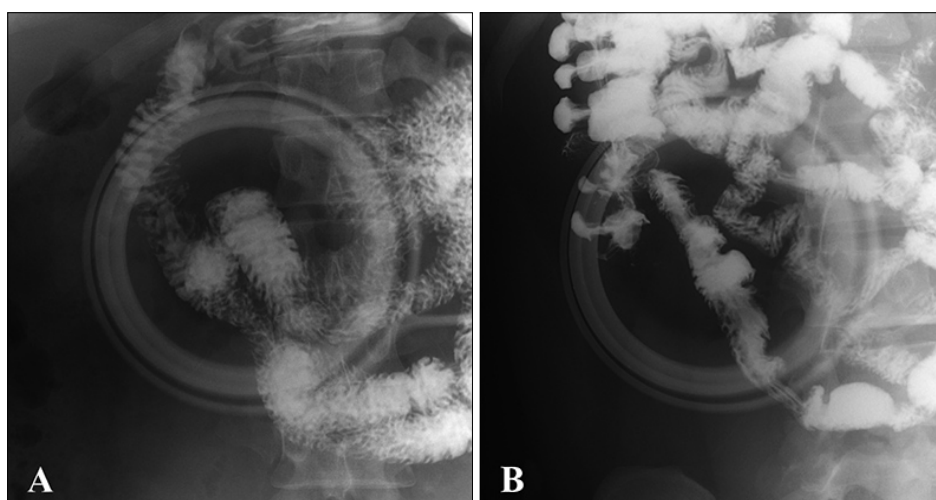


Fig. 4. The small bowel series shows (A) Filling defect lesion on the junction of duodenum 2nd and 3rd portion (2 cm long). (B) No other specific filling defect can be observed in the small bowel loops, especially on the terminal ileum.

keratosis and epidermal proliferation, were noted. Slightly dilated blood vessels in the papillary dermis and a sparse infiltrate of lymphocytes were noted (Fig. 3A, B). Biopsy of small erythematous papules from the forehead showed a plugging of the hair follicle by keratin with typical histologic backgrounds of folliculitis including perifollicular lymphocyte infiltration (Fig. 3C, D).

The small bowel series showed a filling defect lesion, which suggested a localized mass or polyp, on the junction of duodenum 2nd and 3rd portion (2 cm long) (Fig. 4A). No other specific filling defect was observed in the small bowel loops, especially on the terminal ileum (Fig. 4B). On thyroid ultrasonography, several probable benign nodules were noted in the right thyroid gland. Genetic analysis by polymerase chain reaction and direct

sequencing of all nine exons of the *PTEN* gene on chromosome 10q23 was performed. Sequence variation was described according to the recommendations in GeneReviews (www.genetests.org) and Genecard, using an mRNA reference sequence (NM.000314.4). Sequence analysis revealed a heterozygous mutation, c.388C>T (p.Arg130*), in exon 5.

DISCUSSION

The diagnostic criteria for Cowden's disease were proposed by Salem and Steck⁸, who divided the diagnostic features into major criteria, minor criteria, and family history. Our patient was suitable for operational diagnosis of Cowden's disease by biopsy-proven multiple palmoplantar

keratosis according to the criteria of the International Cowden Consortium (Operational Diagnostic Criteria)⁹. These criteria are based on the presence of pathognomonic mucocutaneous lesions with multiple facial trichilemmomas, acral keratosis, mucous lesions, and papillomatous papules. Major and minor features included hamartomas (lipomas, fibromas, or adenomas) of other organs such as breast, thyroid, central nervous system, and gastrointestinal tract⁹.

Mucocutaneous lesions are present in 90% to 100% of Cowden's disease cases so they are a prominent feature of the disease¹. Most often, the characteristic skin signs develop in the 2nd and 3rd decades, but onset age may range from 4 to 75 years¹⁰. Cutaneous signs are usually the first presenting lesions of the disease⁷. Our patient noticed the first skin signs after the age of about 10. Facial papules are the most frequent lesions, can be found in up to 86% of cases, and are preferentially localized in periorificial regions¹⁰. A histologic review of facial lesions associated with Cowden's disease was done by Brownstein et al.¹¹ Many of the patients who underwent histologic examination of facial lesions showed facial trichilemmomas and it was diagnostic¹⁰. The results indicate that most facial lesions belong to a spectrum of follicular abnormalities that include trichilemmomas and tumors of the follicular infundibulum. Our case showed histologic features of folliculitis, a follicular abnormality¹⁰. Oral mucosal papillomatosis were seen in 83% of the patients reviewed⁸. The histology of oral lesions was that of benign fibromas⁸ or inflammatory fibro-epithelial hyperplasia¹. In Salem and Steck's study⁸, palmoplantar keratosis was present in 42% of the reported cases and represented translucent, hard papules on the palms and soles that may show a central depression. The palmoplantar lesions were present in half of the patients reported in the literature, and our patient also showed palmoplantar keratosis confirmed by skin biopsy.

Further associated cutaneous findings include lipomas, hemangiomas, xanthomas, vitiligo, neuromas, café au lait spots, periorificial and acral lentiginos, and acanthosis nigricans¹⁰.

Including cutaneous symptoms, Cowden's disease can involve any organ, but especially breast, thyroid, and gastrointestinal tract¹². In 71% of cases, gastrointestinal polyps accompanied lesions anywhere in the gastrointestinal tract. The pathologic spectrum of the gastrointestinal polyps reported in Cowden's disease includes hamartomatous, juvenile, lipomatous, lymphomatous, inflammatory, hyperplastic, and occasionally adenomatous¹. Also, in our patient, multiple papillomatous lesions in the gastrointestinal tract were confirmed by endoscopic biopsy. If

the breast or thyroid is affected, the condition can easily progress to malignancy, so cautious observation is needed⁶. Our patient showed several probable benign nodules in the right thyroid gland on thyroid ultrasonography. It is known that the thyroid is affected in about 67% of cases. In this case, there was a family history of thyroid cancer (his sibling). Although the lesions are usually benign in nature, further evaluation is recommended⁴.

The cause of Cowden's disease is not known. It is a familial hereditary, autosomal dominant condition with incomplete penetrance⁴. In 1996, Nelen et al.¹³ mapped Cowden's disease locus on the human chromosome.

PTEN, a tumor-suppressor gene, is frequently deleted at chromosome 10q23. PTEN appears to be a frequent mutation target in human tumors associated with genomic instability^{14,15}. PTEN mutations were found to associate with phenotypes characteristic of hamartoma tumor syndromes^{16,17}. Mutations in exons 5, 7, and 8 are likely to alter the phosphatase activity of the protein or result in a truncated protein^{18,19}. Furthermore, biochemical analyses from previous studies have shown that most of the missense mutations found in the phosphatase domain, dramatically decrease or inactivate phosphatase activity¹⁸.

Herein, we report a rare case of sporadic Cowden's disease, in which the patient had positive typical cutaneous features with cutaneous facial papules, oral mucosal papillomatosis, palmoplantar keratosis, and hamartomas of the gastrointestinal tract and thyroid gland. Further regular laboratory and image studies will be planned for our patient, as well as his family members.

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CONFLICTS OF INTEREST

The authors have nothing to disclose.

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