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CASE REPORT

Gastrointestinal polyposis with esophageal polyposis is useful for early diagnosis of Cowden's disease

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Abstract

Cowden's disease, one of the several hamartoma syndromes, is characterized by hyperplastic lesions and hamartomas distributed in the whole body. About thirty percent of patients with Cowden's disease have been reported to be complicated by malignant tumors. Based on the criteria of the International Cowden Consortium, this disease is mainly diagnosed as trichilemmoma of the face and oral mucosal papillomatosis. However, Cowden's disease patients themselves often do not recognize trichilemmoma of the face and oral mucosal papillomatosis. We report a case of Cowden's disease in a 33-year-old female patient who was diagnosed based on the characteristic findings at gastrointestinal endoscopy. Clinically, the patient was aware of having bloody stools. Multiple polyps found endoscopically in the esophagus, stomach, ileum, colon and rectum showed histopathologically hamartomatous changes and epithelial hyperplasia. Physical examination revealed oral papillomatosis and facial trichilemmomas. A germline mutation in exon 8 of the phosphatase and tensin homolog deleted on chromosome ten (*PTEN*) gene was found in this case. It was a point mutation of C to T at codon 1003 (CGA→TGA, arginine→stop codon). The characteristic findings on gastrointestinal endoscopy led us to a diagnosis of Cowden's disease. It has been reported that gastrointestinal polyposis with esophageal polyposis is found in about 85.7% of Japanese patients with Cowden's disease. The characteristic findings on gastrointestinal endoscopy can be a useful diagnostic clue to Cowden's disease.

Key words: Cowden's disease; Gastrointestinal polyposis; *PTEN*; Early diagnosis; Hamartoma

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INTRODUCTION

Cowden's disease was reported for the first time by Lloyd and Dennis in 1963[1]. There have been more than 200 case reports in Japan. Cowden's disease, one of the several hamartoma syndromes, is characterized by hyperplastic lesions and hamartomas distributed on the whole body[2]. About 30% of patients with Cowden's disease have been reported to be complicated by malignant tumors[3]. It was reported that this disease is mainly diagnosed mainly as facial papules and oral mucosal papillomatosis[4] (Table 1). Recently, the criteria of the International Cowden Consortium are commonly used for the diagnosis of Cowden's disease[5] (Table 2). Ninety-nine percent of individuals with Cowden's disease are believed to have developed mucocutaneous lesions at the age of about 30 years[5]. However, Cowden's disease is rarely diagnosed based on the physical findings of typical skin lesions, and the diagnosis of typical

trichilemmoma requires many biopsy specimens[6,7]. Cowden's disease patients themselves often do not recognize the characteristic dermatological findings of Cowden's disease. Furthermore, it is possible that they are not checked for the specific findings of Cowden's disease even when they do notice the lesions[8]. Gastrointestinal polyposis has been reported in about 40% of patients with Cowden's disease in Western countries[9], but it has been reported that this disease is frequently accompanied with gastrointestinal polyposis in Japan[10]. We, here, report a case of Cowden's disease diagnosed based on the characteristic findings at gastrointestinal endoscopy.

CASE REPORT

A 33-year-old female patient had a medical examination at the Department of Internal Medicine, Kurihara Central Hospital, because of bloody stools. The patient underwent total thyroidectomy at the age of 20 years. Her mother died of gastric and breast cancer after she underwent the same operation. The patient was obese with no abnormality in the laboratory data. Colonoscopy showed multiple polyps in the terminal ileum, colon and rectum, which gave the macroscopic appearance of smooth lesions. Moreover, all polyps were within 5 mm in size. All biopsy specimens of these lesions showed epithelial hyperplasia and were diagnosed histopathologically as hyperplastic polyps (Figure 1). Double contrast X-ray study showed multiple small polypoid lesions in the ileum, colon and rectum (Figure 2). Endoscopy of the upper digestive tract showed the presence of whitish polypoid lesions in the esophagus as well as in the stomach and duodenum. Specimens of these polyps were resected by polypectomy. These polyps also had the macroscopic appearance of smooth lesions. Moreover, the size of all these polyps was within 10 mm. The gastric polyps showed hamartomatous changes and epithelial hyperplasia. A specimen was diagnosed as hamartoma by histopathological examination (Figure 3). The esophageal polyps were diagnosed histopathologically as glycogenic acanthosis (Figure 4). Otherwise, no abnormal findings were found both at computed tomography (CT) scan of the abdomen or breast and at abdominal ultrasonography. Papillomatosis of the gingiva was found (Figure 5) in addition to a small papule on the face. It was diagnosed histopathologically as a trichilemmoma by skin biopsy (Figure 6). Genetic analyses performed with informed consent clarified a germline mutation of the phosphatase and tensin homolog was deleted on chromosome ten (*PTEN*) gene (Figure 7). A germline mutation in exon 8 of the *PTEN* gene was found. It was a point mutation of C to T at codon 1003 (CGA→TGA, arginine→stop codon). We diagnosed this patient as Cowden's disease based on the characteristic physical findings and the result of the genetic test described above. This study was approved by the Institutional Ethics Committee of Kurihara Central Hospital.

Table 1 Proposed diagnostic criteria for Cowden's disease

Proposed diagnostic criteria for Cowden's disease
Major clinical criteria
Cutaneous facial papules
Oral mucosal papillomatosis
Minor clinical criteria
Acral keratosis
Palmoplantar keratoses
Family history of Cowden's disease
Definite: 1a+1b,(1a or 1b)+(2a or 2b)
(1a or 1b)+3, 2a+2b+3
Probable: 1a or 1b, (2a or 2b)+3
Possible: 2a and/or 2b

Table 2 Criteria of international Cowden Consortium (Verion 2000) for Cowden's disease

Pathognomonic criteria
Mucocutaneous lesions
Trichilemmomas, facial
Acral keratoses
Papillomatous papules
Mucosal lesions
Major criteria
Breast carcinoma
Thyroid carcinoma (non-medullary), especially follicular thyroid carcinoma
Macrocephaly (megalencephaly) (say, 95th centile)
Lhermitte-Duclos disease (LDD)
Endometrial carcinoma
Minor criteria
Other thyroid lesions (eg, adenoma or multinodular goitre)
Mental retardation (say, IQ 75)
GI hamartomas
Fibrocystic disease of the breast
Lipomas
Fibromas
GU tumours (e.g. renal cell carcinoma, uterine fibroids) or malformation
Operational diagnosis in a person
Mucocutaneous lesions alone if:
There are 6 or more facial papules, of which 3 or more must be trichilemmoma, or
Cutaneous facial papules and oral mucosal papillomatosis, or
Oral mucosal papillomatosis and acral keratoses, or
Palmoplantar keratoses, 6 or more
2 major criteria but one must include macrocephaly or LDD
1 major and 3 minor criteria
4 minor criteria
Operational diagnosis in a family where one person is diagnostic for Cowden syndrome
The pathognomonic criterion/ia
Any one major criterion with or without minor criteria
Two minor criteria

DISCUSSION

Cowden's disease, reported for the first time by Lloyd and Dennis in 1963[1], belongs to a multiple hamartoma syndrome[2], and there have been more than 200 case reports in Japan. The diagnosis of Cowden's disease was originally made b based on the examination of skin and a family history of Cowden's disease[4] (Table 1).

However, the original diagnostic criteria for Cowden's disease were based on dermatological findings. The criteria of the International Cowden Consortium are commonly used for the diagnosis[5] (Table 2). The patient

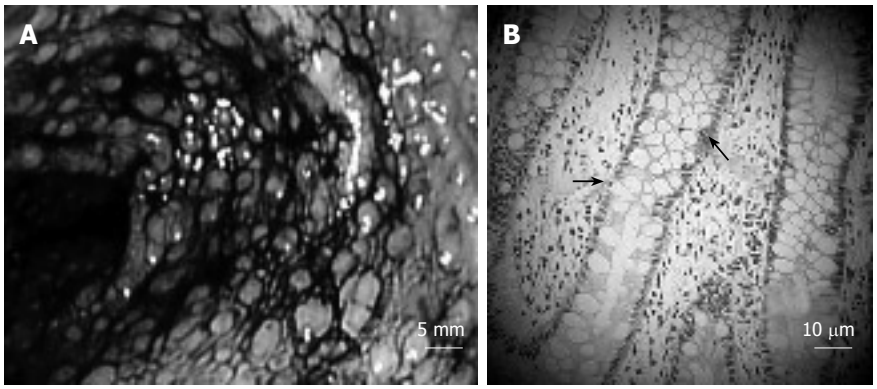

Figure 1 Polyposis in the rectum. **A**: Colonoscopy showing multiple polyps in the terminal ileum, colon and rectum, which gave the macroscopic appearance of smooth lesions. Moreover, the size of all polyps was within 5 mm or smaller; **B**: Pathological appearance of multiple polyps with all biopsy specimens of these lesions showing epithelial hyperplasia. These specimens were diagnosed histopathologically as hyperplastic polyps (arrow).

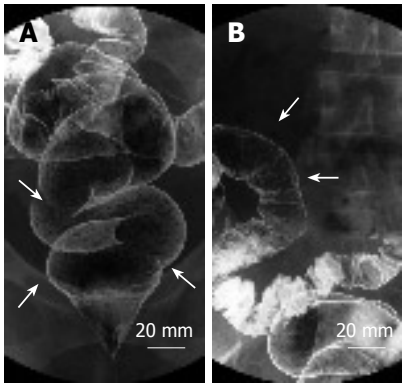

Figure 2 Double contrast X-ray study (**A**) and double contrast X-ray study (**B**) showing multiple small polypoid lesions in the ileum, colon and rectum.

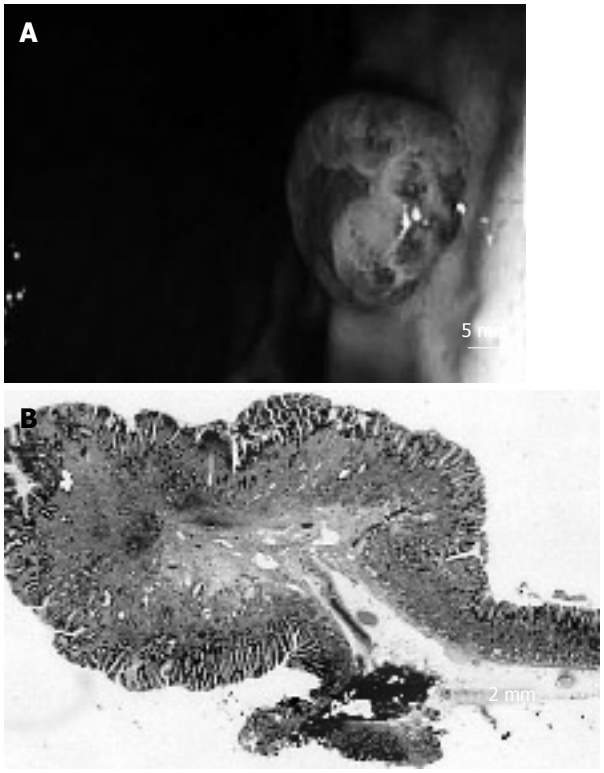

Figure 3 Polypoid lesions in the stomach. **A**: Endoscopy of the upper digestive tract showing whitish polypoid lesions in the stomach. The size of all these polyps was within 10 mm; **B**: Gastric polyps showing histopathologically hamartomatous changes and epithelial hyperplasia. A specimen was diagnosed as a hamartoma by histopathological examination.

was diagnosed as trichilemmoma and oral papillomatosis, thyroid tumor and gastrointestinal hamartoma. This case fulfilled both diagnostic criteria for this disease. Moreover, the patient's mother also had a history of total thyroidectomy and died of gastric and breast cancer. We think that her mother suffered from Cowden's disease, based on the criteria of the International Cowden Consortium.

The criteria of the International Cowden Consortium are useful for diagnosis of Cowden's disease, but such criteria may not be useful for its early diagnosis. Although we diagnosed a case of Cowden's disease based on the criteria of the International Cowden Consortium, we did not recognize the facial papules and oral mucosal papillomatosis at the first examination. The patient also did not recognize them. At first, we considered the possibility that this case was Cowden's disease because of her history of thyroid goiter and the finding of gastrointestinal polyposis including esophagus at gastrointestinal endoscopy. Later, detailed physical examination revealed oral papillomatosis and a small papule of the face. We made a histopathological diagnosis of trichilemmoma. Ninety-nine percent of individuals with Cowden's disease are believed to have mucocutaneous lesions at the age of about 30 years[9]. However, it has been reported that it is difficult to diagnose Cowden's disease only based on the physical finding of a typical trichilemmoma and in fact that it requires many biopsy specimens[6,7]. Cowden's disease patients themselves often do not recognize the characteristic dermatological findings of Cowden's disease. Furthermore, it is possible that they are not checked for the specific findings of Cowden's disease even when they do notice them[8,11].

Gastrointestinal endoscopy is more frequently performed in Japan. Recently, we have often diagnosed Cowden's disease based on the characteristic findings at gastrointestinal endoscopy[12]. It was reported that gastrointestinal polyposis occurs in about 40% of Cowden's disease patients in Western countries[9], but in Japan it occurs in about 95% of Cowden's disease patients[10]. Gastrointestinal endoscopy and double contrast X-ray study endoscopy and double contrast X-ray study can detect gastrointestinal polyposis showing histopathologically hamartomatous changes and

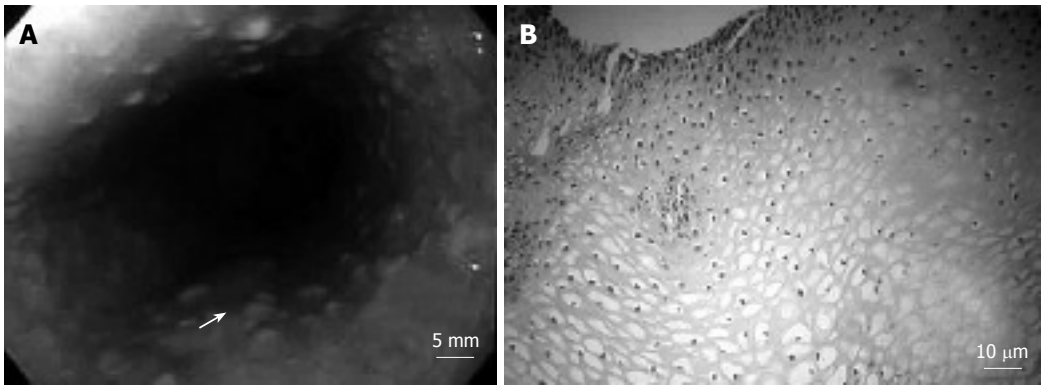

Figure 4 Polypoid lesions in the esophagus. **A**: Endoscopy of the upper digestive tract showing whitish polypoid lesions in the esophagus and macroscopic appearance of smooth lesions. The size of all these polyps was within 5 mm; **B**: Pathological appearance of the esophagus. Histlogically, a specimen confirmed the diagnosis of glycogenic acanthosis.

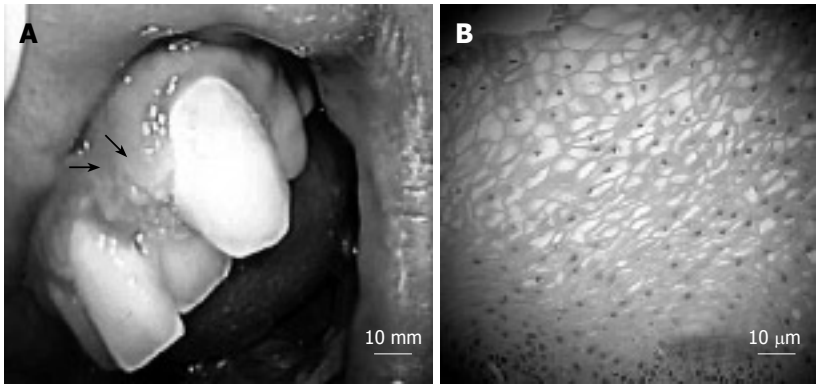

Figure 5 Many polyps in the gingiva (**A**) and pathological appearance of the gingiva confirming the diagnosis of papilloma(**B**).

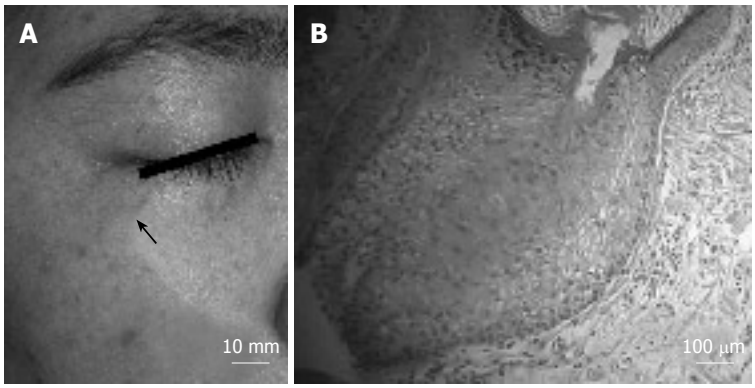

Figure 6 Small papules found on face with their size within 5 mm (**A**) and pathological appearance of small papules confirming the diagnosis of trichilemmoma (**B**).

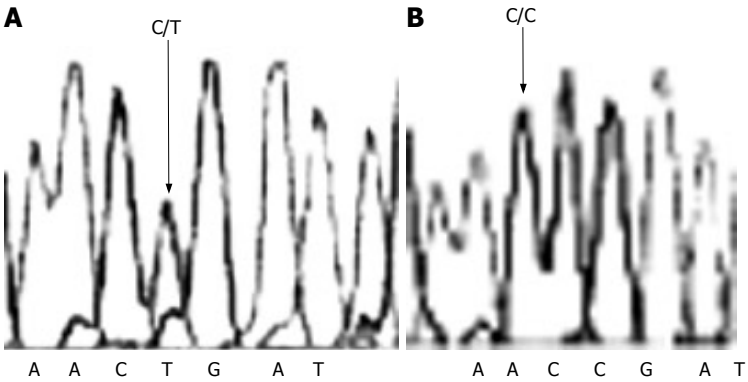

Figure 7 A germline mutation of phosphatase and tensin homolog deleted on chromosome ten (*PTEN*) gene. **A**: Genetic analyses performed with informed consent clarified a germline mutation of the *PTEN* gene in exon 8 of the *PTEN* gene, which was a point mutation of C to T at codon 1003 (CGA→TGA, arginine→stop codon); **B**: Control.

epithelial hyperplasia. Esophageal polyposis found in 85.7% of Cowden's disease patients[10], is a characteristic finding in young patients with Cowden's disease[13,14]. Esophageal polyposis shows histopathologically glycogenic acanthosis[14]. In addition to Cowden's disease, other types of gastrointestinal polyposis

include familial adenomatous polyposis, Peutz-Jeghers syndrome and Juvenile polyposis, which, however, do not show esophageal polyposis[13,14]. Multiple polyps found endoscopically in the esophagus, stomach, ileum, colon and rectum of the present case, showed histopathologically hamartomatous changes and epithelial hyperplasia, suggesting that this case fulfills the diagnostic criteria for Cowden's disease. Gastrointestinal and esophageal polyposis is not described in the criteria of the International Cowden Consortium. However, the characteristic gastrointestinal findings are useful for early diagnosis of Cowden's disease.

In the present case, a germline mutation found in exon 8 of the *PTEN* gene was a point mutation of C to T at codon 1003 (CGA→TGA, arginine→stop codon). Germline *PTEN* mutations were first described in Cowden's disease. The *PTEN* gene encodes a lipid phosphatase on 10q23 that mediates cell cycle arrest and apoptosis. Germline *PTEN* mutations are not described in the criteria of the International Cowden Consortium, but are found in 80% of Cowden's disease patients[12,15-17], indicating that Germline *PTEN* mutations may be useful for the surveillance of Cowden's disease.

In the present case, we could not find any malignant diseases. However, because about 30% of Cowden's disease patients have been reported to be complicated by malignant tumors, early diagnosis of Cowden's disease is necessary[3,9,18]. Recently, 18-fluoro-deoxyglucose positron emission tomography has become useful for cancer surveillance in Cowden's disease patients. We expect that sensitive molecular diagnostic tests for mutations in appropriate genes will become clinically available in the setting of cancer genetics consultation[19].

In summary, we report a case of Cowden's disease diagnosed based on the characteristic findings at gastrointestinal endoscopy. Gastrointestinal and esophageal polyposis is useful for the early diagnosis of Cowden's disease, and the characteristic findings at gastrointestinal endoscopy can be considered useful diagnostic clues to Cowden's disease.

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