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CASE REPORT

Ganglioneuromatosis of the Colon and Extensive Glycogenic Acanthosis in Cowden's Disease

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Cowden's disease is a rare genetic disease characterized by tumor development in many organs. In most, tumors are benign, appear in the third to fourth decade (1) and are most commonly seen in the face, the thyroid, and the gastrointestinal tract. Breast cancer, seen in nearly 50% of female patients with the disease, represents the major prognostic risk factor (2). Cowden's disease itself has been considered a marker for breast cancer (3).

The current case report is of a 51-year-old woman whose illness is characteristic of Cowden's disease. The specific pattern of gastrointestinal involvement seen in this patient, however, has not been reported. The patient has extensive glycogenic acanthosis of the esophagus, submucosal fibrosis of the stomach, gastric heterotopia in the duodenum, and ganglioneuromatosis of the colon.

CASE REPORT

A 51-year-old female was referred for evaluation of dysphagia. She was well until age 25 when she began to develop multiple tiny polypoid lesions around her mouth. These lesions required periodic removal. At age 30, investigation of rectal bleeding revealed multiple rectal polyps; no biopsy specimens were available for review. At age 36 the patient had a subtotal thyroidectomy for a goiter, biopsy specimens of which were unavailable. She currently requires thyroid hormone replacement. A nonmalignant vascular tumor was removed from the right hand at age 47. Symptoms of dysphagia include an intermittent sensation of obstruction at the base of the neck and pharyngoesophageal bolus transit difficulties. Heartburn and hematemesis have not occurred. There is a history of bilateral cataracts and left ear tinnitus.

The patient's grandmother and the patient's sister both died of breast cancer in their fourth decade. There is no family history of facial polypoid lesions or of Cowden's disease.

On physical examination the patient had multiple soft, small flesh-colored polypoid lesions on the face, congregated around the mouth, nose, and ears. The tongue had similar polypoid lesions on its surface. There was a hypoplastic mandible and a prominant forehead. Bilateral cataracts were noted on ophthalmoscopic examination. There were no palpable masses in the breasts but there were multiple seborrheic keratoses on the undersurface. There was no residual palpable thyroid tissue. The remainder of the physical examination was unremarkable.

Upper gastrointestinal endoscopy revealed multiple small polyps in the hypopharynx probably accounting for the patient's dysphagia. These were not biopsied. There were also multiple slightly raised plaquelike lesions in the esophagus covering most of the mucosa which were more white than surrounding normal-appearing mucosa (Figure 1). Proximally the lesions were nearly confluent, becoming more discrete in the distal esophagus. Biopsies documented the changes consistent with glycogenic acanthosis (Figure 2). Esophageal manometry was normal. About 10 polypoid lesions were seen along the greater curvature of the stomach which were believed to be formed by submucosal fibrosis covered with normal epithelium. Three duodenal lesions were also noted which on biopsy proved to be heterotopic gastric mucosa.

A small bowel roentgenogram failed to reveal any polypoid lesions, but colonoscopy demonstrated two types of abnormalities. There was in the cecum an isolated 5-mm polyp which proved histologically to be a tubular adenoma. The rectosigmoid region was carpeted with multiple 2- to 3-mm sessile polypoid lesions (Figure 3), biopsies of which revealed ganglioneuromata scattered throughout the lamina propria (Figures 4 and 5).

Clinically the patient is doing well. Dysphagia is resolving with conservative therapy. No breast lesions have become evident on physical examination or on mammography.

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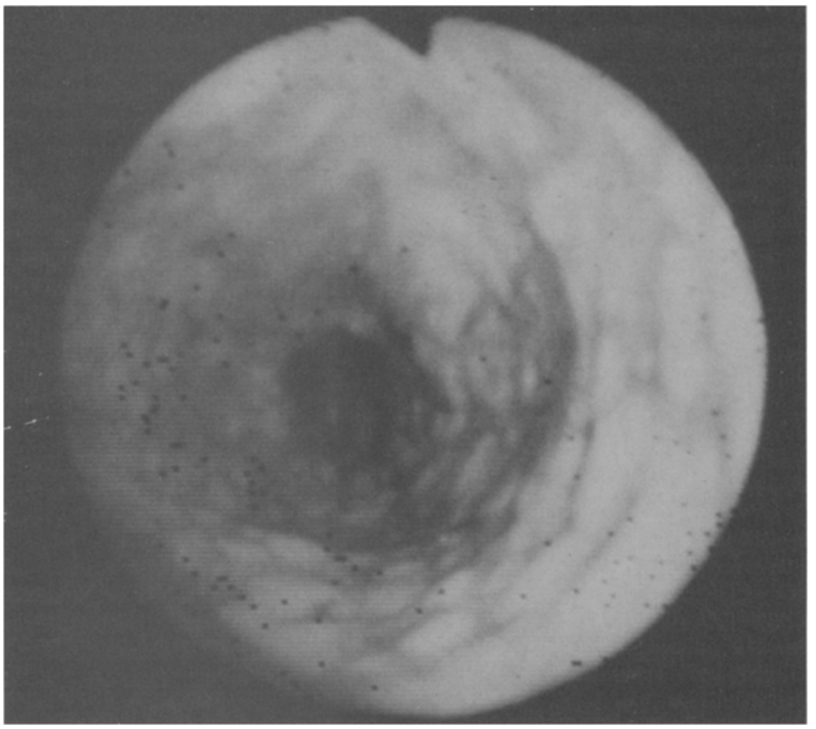

Fig 1. Upper endoscopy showing multiple pale plaquelike lesions in the upper esophagus. The lesions measured 2–3 mm in diameter.

DISCUSSION

Cowden's disease is a heterogenous genetic disorder characterized by multiple hyperplastic and neoplastic tumors involving various areas of the body. Also called the multiple hamartoma syndrome, the disease was first described in 1963 of a patient, whose surname was Cowden, with multiple genetic abnormalities (4). Nine years later case reports of similar patients began to appear in the literature (5), and to date over 50 cases have been reported. As more cases have become recognized, clinical characteristics and criteria for diagnosis have become better defined. The disease has been reported in three generations of the same family with no sex linkage (6). Autosomal dominant inheritance is believed to be the mode of transmission. A characteristic feature of the disease is facial trichilemmomas, benign tumors of follicular epithelium. These occur predominantly around the mouth, eyes, nose, and ears. When coupled with a hypoplastic mandible and a prominant forehead, they give patients with Cowden's disease a characteristic facies, which has become a marker of disease (7, 8).

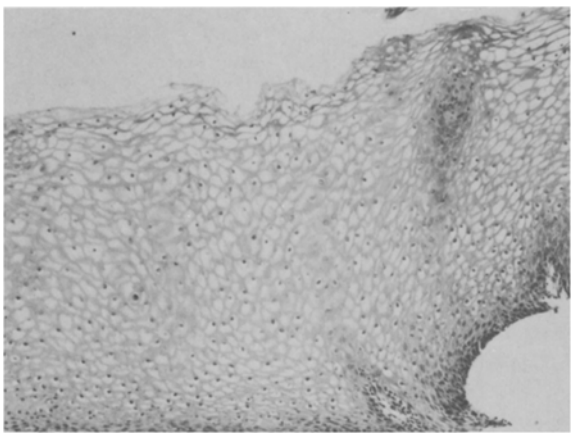

Fig 2. Esophageal biopsy showing enlarged vacuolated cells that contained increased glycogen (PAS-positive, diastase-sensitive material) as seen in glycogenic acanthosis. H&E, ×80.

Patients with Cowden's disease have a high incidence of tumors elsewhere in the body. The most frequent locations are the breast, the thyroid, and the gastrointestinal tract. Most female patients have fibrocystic disease of the breast. Malignant disease of the breast is seen in as many as 50% of female patients (2) but has not been reported in males. It has been suggested that Cowden's disease is a marker for malignant disease of the breast and

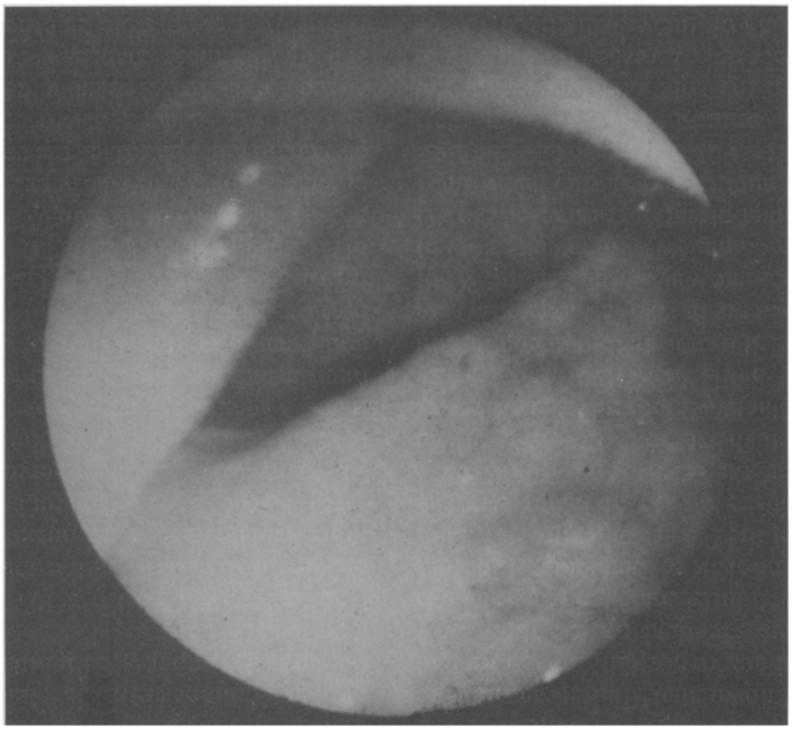

Fig 3. Colonoscopy showing multiple small polypoid lesions in the sigmoid colon measuring 2–3 mm in diameter.

should prompt vigorous screening or prophylactic surgery (3). Thyroid diseases reported include goiter, adenoma, carcinoma, and acute thyroiditis, but the thyroid is not a major source of morbidity.

Gastrointestinal manifestations of Cowden's disease have been reported in every area of the alimentary canal. Most commonly polyps of different types have been observed. Glycogenic acanthosis of the esophagus, lymphoid and hyperplastic polyps of the stomach, small bowel polyposis, and adenomatous, inflammatory, lipomatous, and neuromatous polyps of the colon have all been reported (9).

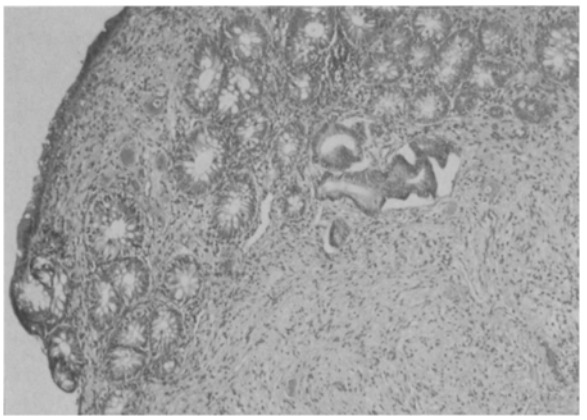

Fig 4. Biopsy of colonic polyp showing replacement of lamina propria by neuronal tissue including ganglion cells. Similar tissue is also present in the submucosa. H&E, ×100.

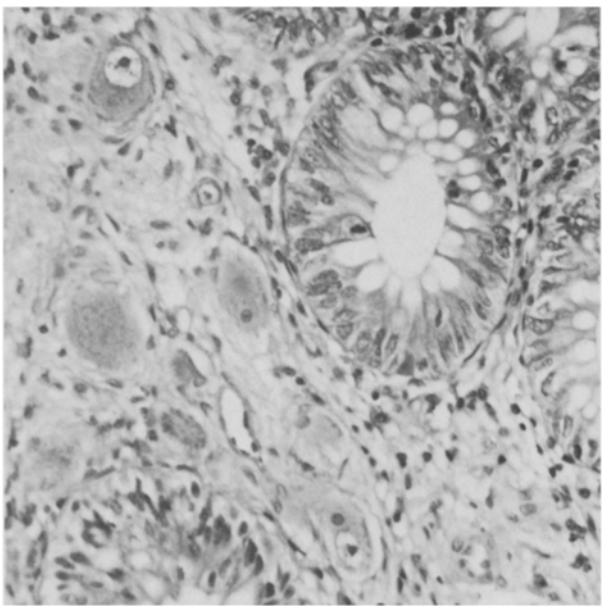

Fig 5. Detail of top left corner of Figure 4 showing ganglion cells between crypts. They have large vesicular nuclei, prominent nucleoli, and Nissl granules in the cytoplasm. H&E, ×310.

Malignancy arising from the digestive tract is not common. One case of adenocarcinoma of the cecum has been reported in a patient with Cowden's disease who also had a neuroma of Auerbach's plexus (10). Gastrointestinal disease is believed to occur in about one third of patients. However, this frequency is most likely an underestimate since the gastrointestinal tract was not carefully examined in all reported patients. Gastrointestinal pathology is not a major determinant of prognosis.

Ganglioneuromata of the colon are seen in a variety of disorders. Lesions represent a conglomerate of Schwann cells and ganglion cells and are present in such diseases as the multiple endocrine neoplasia type IIb syndrome and von Recklinghausen's disease. Patients are frequently troubled by diarrhea and/or constipation but the pathophysiology of these symptoms has not been elucidated (11).

The current case report represents the fourth known case of ganglioneuromatosis of the colon in a patient with Cowden's disease. The first was reported in a 32-year-old woman with four varieties of colonic polyps (5). The second was in a 53-year-old man with a single neuroma of Auerbach's plexus who developed cecal carcinoma (10). The third was in a 28-year-old male with rectosigmoid ganglioneuromatosis (9). To date, no consistent pattern of gastrointestinal disease involving ganglioneuromatosis in Cowden's disease has emerged. Perhaps with continued case reporting, patterns of gastrointestinal pathology in Cowden's disease will be better understood.

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