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Cowden's Disease: A Case Report and Literature Review

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Abstract. Cowden's disease, or multiple hamartoma syndrome, is an uncommon condition with characteristic mucocutaneous lesions associated with abnormalities of the breast, thyroid, and gastrointestinal tract. We describe a 51-year-old man with hyperplastic polyposis of the entire alimentary tract as the most prominent feature of this disease. We also present a review of 85 cases of this entity as reported in the English medical literature, and summarize the pertinent findings.

Key words: Cowden's disease, diagnosis – Gastrointestinal polyposis.

Cowden's disease is inherited as an autosomal dominant condition and is characterized by multiple hamartomatous malformations of the endodermal, mesodermal, and ectodermal layers. Although gastrointestinal polyposis is a common feature of Cowden's disease, its prevalence is difficult to estimate from the literature because gastrointestinal examinations were done in only about half of the patients reported. We describe a 51-year-old man with this disease who had polyposis involving the entire alimentary tract, and we review the English language literature on Cowden's disease.

Case Report

A 51-year-old man was admitted for his yearly evaluation of polyposis of the alimentary tract, and denied the presence of gastrointestinal symptoms. He had had a partial thyroidectomy for a goiter at age 16. At age 25, multiple skin tags of both axillae and the upper thighs were noted. Ten years later, the patient complained of hematochezia and multiple 1–3-mm polyps were found in the stomach by gastrocamera and in the rectum by sigmoidoscopy. Multiple polyps were demonstrated in the entire alimentary tract the following year by radiographic and endoscopic examinations. The polyps removed were hyperplastic pathologically. For the last 15 years the patient has been examined radiographically or endoscopically at least yearly. Multiple biopsies and histologic examinations of his gastric and colonic polyps have shown them to be of hyperplastic or chronic inflammatory origin. Family history disclosed that 1 brother had identical skin lesions and polyps. His mother had similar skin tags. Three other brothers refused evaluation.

On physical examination, multiple skin tags measuring 2–10 mm were present in the axillary and inguinal areas. A 1.0-cm pedunculated lesion on the left axilla and a small tag on the left wrist that were removed were shown to be a fibroepithelial polyp and a neurofibroma, respectively. There were several areas of poorly defined hyperpigmentation on the lower lip. Several warts were found on the hands. Several small polyps were palpated by digital rectal examination.

A double-contrast upper gastrointestinal series showed numerous small polyps up to 4 mm distributed throughout the esophagus (Fig. 1 A). Multiple gastric polyps up to 1 cm were found (Fig. 1 B). The polyps were fewer and smaller in the duodenum. Enteroclysis showed multiple small polyps throughout the small bowel, predominantly in the proximal jejunum (Fig. 2). A double-contrast barium enema showed multiple small polyps throughout the colon, with the greatest number in the rectosigmoid region (Fig. 3). Upper gastrointestinal endoscopy confirmed numerous pearly white polyps 1–3 mm throughout the esophagus, stomach, and duodenum. Histologic examination of a biopsy specimen revealed marked subacute and chronic inflammation. Colonoscopy showed numerous 2–3-mm polyps throughout the colon. A 1-cm polyp was removed from the hepatic flexure, and was seen to be hyperplastic when examined pathologically.

Discussion

Multiple hamartoma syndrome, or Cowden's disease, is a rare cause of intestinal polyposis. It was first described by Lloyd and Dennis [1] in 1963 and named after the first patient reported. Cowden's disease is inherited as an autosomal dominant condition and is characterized by multiple ha-

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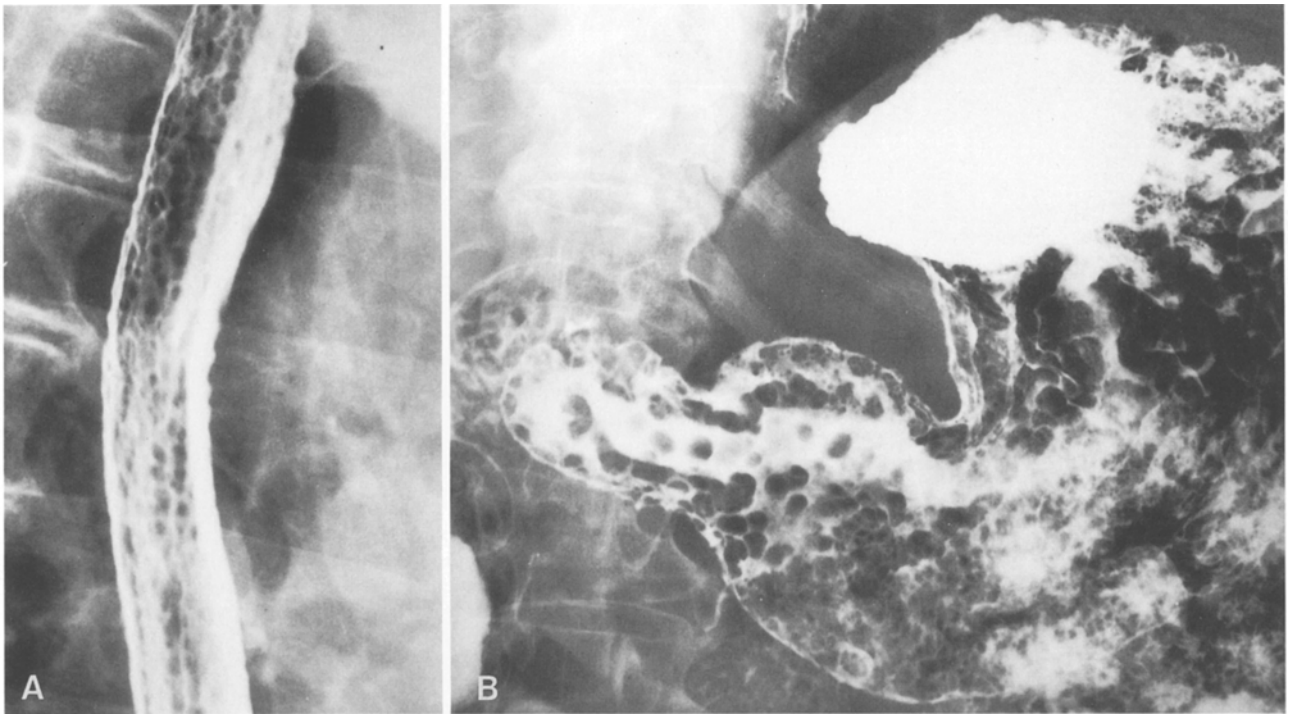

Fig. 1. Upper gastrointestinal series in Cowden's disease. **A** Innumerable polyps measuring up to 4 mm cover the entire esophagus. **B** Diffuse gastric polyps of various sizes up to 1 cm and more numerous in the antrum.

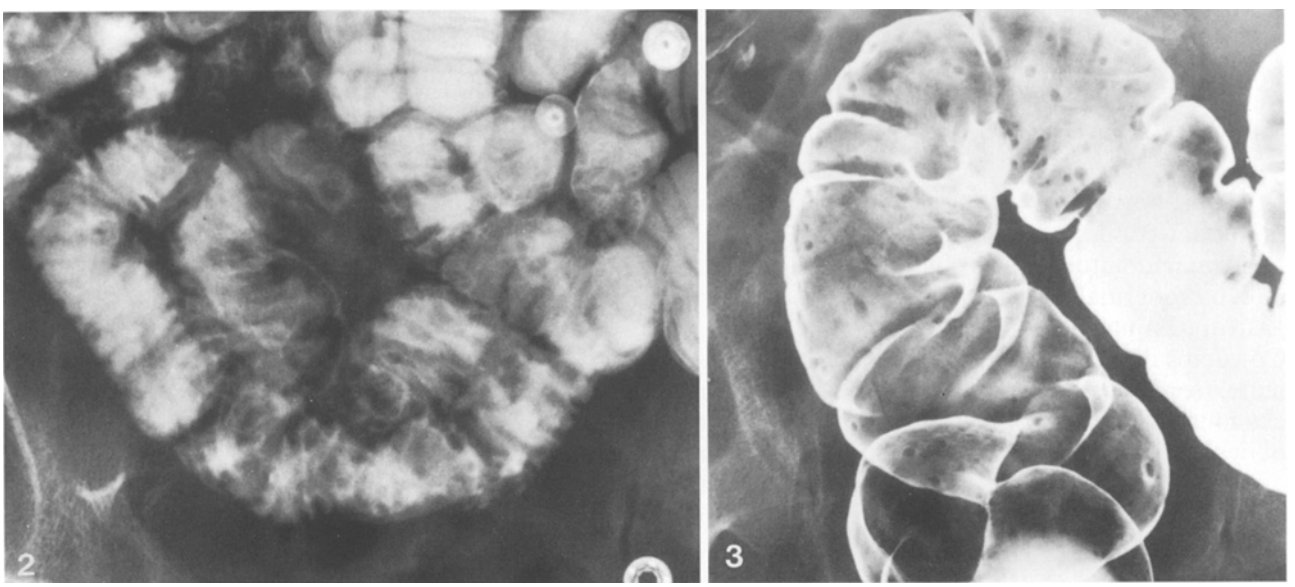

Fig. 2. Enteroclysis shows scattered polyps in the pelvic small bowel loops, producing a nodular mucosal pattern.

Fig. 3. Double-contrast examination of rectosigmoid colon demonstrates numerous small polyps.

martomatous malformations affecting the skin, mucous membranes, and internal organs. Other associated abnormalities include thyroid tumor, gastrointestinal polyposis, neurologic abnormalities, and angiomatous malformations. Since 1963, 85 cases have been reported [1–35] in the English literature and are summarized in Table 1. Positive family histories were present in 43 patients from 23 families.

Cowden's disease was initially discovered in

Table 1. Summary data in 85 patients with Cowden's disease

Date reported	Sex M/F	Associated lesions of				Alimentary tract lesions					Family/ cases
		Skin	Mouth	Thyroid	Breast	Esoph.	Stomach	Sm. bowel	Colon	Misc.	
1963	0/ 1	1	1	1	1					1	1/1
1972	1/ 4	5	4	5	4		1		2	3	1/1
1974	5/ 3	8	6	3	3				2	2	1/7
1975	2/ 4	6	5	4	4				2	2	3/4
1977	1/ 3	4	4	3	2				1	1	1/1
1978	5/ 6	11	8	5	6	1	3	1	1	5	3/5
1980	6/ 3	9	8	6	3	3	4	5	5	4	3/3
1981	5/ 3	8	6	6	4				4	4	2/3
1982	0/ 1	1	1	1	1					1	—
1983	2/ 3	5	5	5	2		1			2	1/3
1984	4/14	18	16	13	7	4	5	5	10	7	4/8
1985	2/ 6	8	8	5	2		1	3	2	3	2/6
1986	1/ 0	1	1	1		1	1	1	1		1/1
Total	34/51	85	73	58	39	9	16	15	30	35	23/43

most patients because of their skin lesions, and these patients were most often reported in the dermatologic literature. The mucocutaneous lesions are considered the most characteristic finding, and have served as a convenient external marker of the disease. Numerous small papular hyperkeratoses, measuring 1–4 mm have been observed on the face, especially around the mouth, nose, eyelids, and ears. Papillary lesions have also been found on the buccal mucosa, gingiva, palate, scrotum, and extremities in many cases. The histopathologic spectrum of these cutaneous papules has been broad, and diagnoses have included trichilemmoma, acanthoma, verruca vulgaris, fibroma, keratosis pilaris, lipoma, fibroangioma, angiolipoma, cavernous hemangioma, and cysts. The type and extent of cutaneous lesions have varied considerably among patients reported.

Alimentary tract abnormalities are common in Cowden's disease, and primarily appear as gastrointestinal polyps. The true prevalence of polyposis in this disease is not known because radiographic and endoscopic examinations of the gastrointestinal tract were done in only 45 (53%) of the 85 cases. Thirty-five patients underwent radiographic or endoscopic examinations of both the upper gastrointestinal tract and colon. The remaining 10 patients underwent only a barium enema. Polyps were present in 32 (71%) of 45 patients examined. Unfortunately, many patients and their relatives refused examination of the gastrointestinal tract.

The distribution of polyps and other abnormalities in the gastrointestinal tract included 9 cases in the esophagus, 16 in the stomach, 14 in the small bowel, and 27 in the colon (Table 2). Of 45 patients

Table 2. Distribution of polyposis and other abnormalities in the alimentary tract in 32 patients with Cowden's disease

Number	Esophagus	Stomach	Small bowel	Colon
4		X		
1			X	
14				X
1	X		X	X
4		X	X	X
8	X	X	X	X

reported undergoing an upper gastrointestinal series and/or barium enema, 9 were normal, and polyps were isolated to the stomach, small bowel, or colon in 4, 1, and 14 cases, respectively. In 13 patients, polyps were found in multiple organs of the alimentary tract. Involvement of the entire digestive tract, as seen in our patient, occurred in 8 of these 13 patients, with 1 patient also having carcinoma of the colon. In the remaining 4 patients, colonic carcinoma was present in 2, colonic diverticulosis in 1, small bowel ulcer in 1.

In the 9 patients with esophageal involvement, numerous polyps measuring 1–4 mm were seen, with 1 case resembling glycogenic acanthosis pathologically [20]. In the stomach, multiple polyps varying in size from 1 mm to 3 cm were found. The duodenum was the most common location for polyps in the small bowel, although the entire organ, including the terminal ileum, may be affected. The colon was the most common gastrointestinal site involved. Colonic polyps and other abnormalities were found in 30 (67%) of 45 patients having barium enema, with 27 patients having polyposis.

Although 3 cases of colonic carcinoma (2 isolated, 1 associated with polyps) have been reported, the incidence of malignant transformation of the gastrointestinal polyps in Cowden's disease remains uncertain. Our patient has been evaluated for 15 years without evidence of colonic malignancy.

The pathologic spectrum of the gastrointestinal polyps reported in Cowden's disease has included juvenile, lymphomatous, hamartomatous, hyperplastic, inflammatory, and occasionally adenomatous types. In a patient with multiple colonic polyps, the differential considerations in addition to Cowden's disease include familial polyposis, Gardner syndrome, Peutz-Jeghers syndrome, Cronkhite-Canada syndrome, and multiple adenomatous polyps [36–41]. Other gastrointestinal lesions may also be encountered, such as pararectal abscess, gastric ulcer, cholecystitis, and hepatic hamartoma [1, 2, 28, 35].

Breast disease is a frequent abnormality in women with Cowden's disease. Thirty-eight (75%) of 51 women and 1 man have had fibrocystic dysplasia of the breast. Breast cancer is common and was found in approximately half of the women with breast disease. Thyroid abnormalities were frequently seen in Cowden's disease: reported in 58 (68%) of 85 cases reviewed. These included goiter, adenoma, carcinoma, and other less common abnormalities. Other abnormalities seen have included supernumerary digits, high-arched palate, deeply-fissured tongue, mandibular hypoplasia, pectus excavatum, scoliosis, bone cysts, meningioma of the ear, thyroglossal duct, and hydrocele [1, 2, 14].

Although our patient had many of the manifestations of Cowden's disease, including goiter, skin lesions, and diffuse gastrointestinal polyposis, their recognition occurred over a 19-year period. This is not unusual since some patients reported with Cowden's disease were initially diagnosed years after the appearance of their first symptom or sign [10–12, 15, 26, 27]. Because multiple polyps of the alimentary tract are frequently seen in Cowden's disease, their occurrence in association with skin, thyroid, and breast lesions should raise the possibility of multiple hamartoma syndrome.

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