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Case study

Colonic ganglioneuromatous polyposis and metastatic adenocarcinoma in the setting of Cowden syndrome: a case report and literature review

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Summary Cowden syndrome is a rare, autosomal-dominant, multisystem disorder characterized by hamartomatous tissue overgrowth and an increased risk of breast, thyroid, and endometrial cancers. Most of the cases arise from germline mutations of the *phosphatase and tensin homologue* tumor suppressor gene. An association with colon cancer remains unproven but has been suggested in previous reports. We present the case of a 42-year-old man with colonic ganglioneuromatous polyps and an adjacent colonic adenoma giving rise to a signet-ring adenocarcinoma with lymph node metastases in the setting of Cowden syndrome. Although gastrointestinal polyps are a common feature of Cowden syndrome, reports of ganglioneuromatous polyps and malignant degeneration are rare. Cutaneous features of Cowden syndrome in our patient include "cobblestone" lesions of the tongue and oral mucosa, facial trichilemmomas, multiple acral keratoses, and a storiform collagenoma.

1. Introduction

Cowden syndrome (CS) is an autosomal-dominant disorder characterized by multiple hamartomas and an increased risk of malignancies that affects 1 in 200 000 to 250 000 people [1]. First recognized in the 1940s, the disease was named in 1963 for a 20-year-old Ohio woman with oral papillomatosis, multiple thyroid adenomas, bilateral breast cancer, and a family history of similar neoplasms [2]. Since that time, associations with breast and endometrial cancers (25%-50% and 5%-10% of female patients, respectively) and thyroid cancer (3%-10% of patients) have been firmly established [1]. Gastrointestinal (GI) pathology, predominantly in the form of nonadenomatous polyps, is present in at least 60% of patients [3]; however, CS-related colon cancer, previously described in isolated case reports, has only recently been examined in larger series [4,5]. We report the case of a 42-year-old man with ganglioneuromatous polyposis who developed a signet-ring adenocarcinoma in an adenomatous polyp that metastasized to regional lymph nodes in the setting of CS. Portions of this case were described previously by Kanter et al [6] before the diagnosis

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of CS based on the discovery of a pathologic *phosphatase and tensin homologue* (*PTEN*) nonsense mutation and recognition of pathognomonic mucocutaneous features.

2. Case Report

This case involves a 42-year-old white man who presented to his primary care physician with painless rectal bleeding. A colonoscopy revealed intestinal polyposis, and biopsy was diagnostic of ganglioneuroma. The patient elected to undergo prophylactic colectomy. The gross colectomy specimen contained an adenomatous polyp, in addition to multiple, finger-like polyps and mesenteric lipomas (Fig. 1A). Microscopic examination of the finger-like polyps was again diagnostic for ganglioneuromatosis (Fig. 1B, C). Examination of the adenomatous polyp was diagnostic for signet-ring adenocarcinoma (Fig. 1D, E). Metastases were detected in 3 of 17 pericolic lymph nodes (Fig. 1F), and the patient was staged T1N1 by AJCC criteria. Eight years postcolectomy, the patient was doing well without disease progression and was referred to dermatology for evaluation of cutaneous lesions. Skin examination revealed multiple pathognomonic features of CS, including acral keratoses, central facial keratotic papules, and oral mucosa and tongue with "cobblestone" lesions. A firm, 1-cm polypoid mass on the abdominal wall was also noted. Family history of similar lesions, colon cancer, or heritable neoplastic syndromes was negative, although the patient's son was noted to have macrocephaly, a minor diagnostic criterion of CS. Genetic testing revealed a pathologic nonsense mutation at the *PTEN* locus.

3. Discussion

Nearly 10 years after Lloyd and Denis published their account of the Cowden kindred, Weary et al [7] described the disorder as "multiple hamartoma syndrome" in a small case series, highlighting CS's defining clinical feature. Today, the diagnosis of CS is made based on clinical criteria maintained by the International Cowden Consortium and the National Comprehensive Cancer Network [1]. Mucocutaneous lesions—including facial trichilemmomas, oral papillomatosis, and acral keratoses—are present in virtually all patients and, in sufficient numbers, are considered pathognomonic for CS. Breast cancer, non-medullary thyroid cancer, cerebellar gangliocytomas, and macrocephaly are considered "major" diagnostic criteria, whereas "minor" criteria include benign thyroid pathology, mental retardation, GI hamartomas, lipomas, fibromas, and genitourinary tumors.

Early investigators believed that GI involvement—most commonly hamartomatous colorectal polyps, but also esophageal glycogenic acantholysis—was present in 40% to 60% of patients with CS, but more recent studies suggest the incidence may approach 85% when asymptomatic individuals are included in endoscopic screening [7,8]. Polyps may be found throughout the GI tract, most frequently in the colon distal to the hepatic flexure, but also in the esophagus, stomach, and small bowel. Histologic subtypes vary, and precise histologic diagnosis can be complex. Hamartomatous polyps are most commonly reported, but leiomyomatous, hyperplastic, lipomatous, and lymphoid varieties have also been described [8]. Reports of ganglioneuromatous polyps are quite rare [9]. When present in patients with CS, they may appear as ganglioneuromatous polyposis with 20 or more small discrete nodules, rather than the larger, less well-demarcated, diffuse ganglioneuromatosis commonly associated with neurofibromatosis and multiple endocrine neoplasia type IIb [10].

Until recently, only a handful of case reports described colon cancer arising in the setting of CS. However, Heald et al [4], in a prospective study of 127 *PTEN* mutation carriers, most of whom met relaxed International Cowden Consortium diagnostic criteria for CS, report that 9 (13%) of 65 patients undergoing colonoscopy were diagnosed with colorectal cancer, all before the age of 50 years. Another recent review reports a 16% lifetime risk of colorectal cancer in patients with CS [5]. Patients with multiple adenomatous or hyperplastic polyps had the highest incidence of malignancy in the Heald study (20% and 15%, respectively). Several cases of non–CS-related ganglioneuromatous polyposis developing into adenocarcinoma have been reported [6,11], leading Kanter et al [6] to suggest the condition be considered premalignant.

Histologic examination of CS-related colonic polyps typically reveals discrete 1- to 2-cm nodules with myofibroblastic expansion of the lamina propria. Crypts are often arranged in lobules and may be surrounded by fibroblasts and myofibroblasts in an onion-skin pattern [12]. Ganglioneuromatous polyposis, when present, is typically characterized by numerous sessile or pedunculated mucosal and/or submucosal lesions with varied proportions of neural, supportive, and ganglion cell content [10]. Polyps may be nodular or filiform in shape, as in the present case. Immunohistochemical staining is generally positive for S-100, neuron-specific enolase, neurofilament protein, and other markers of neural crest origin, but diagnosis can often be made by identification of ganglion cells with hematoxylin and eosin stain [13]. Markers of malignant progression are similar to those found in more common settings of sporadic and familial adenocarcinoma.

In addition to GI polyps, our patient exhibited multiple cutaneous hamartomas—including facial trichilemmomas, oral cobblestone lesions, acral keratoses, and a storiform collagenoma—that met diagnostic criteria for CS [1]. Genetic testing revealed a nonsense mutation of the *PTEN* tumor suppressor at chromosome 10q22-23 [14]. Intragenic or promoter *PTEN* mutations have been detected in as many as 85% of patients with CS [15], among the highest