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Hamartomatous polyps of the colon - Ganglioneuromatous, stromal, and lipomatous

Permalink
https://escholarship.org/uc/item/85v9m19r

Journal
Archives of Pathology & Laboratory Medicine, 130(10)

ISSN
0003-9985

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Publication Date
2006-10-01

Peer reviewed
Hamartomatous Polyps of the Colon
Ganglioneuromatous, Stromal, and Lipomatous

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● Intestinal ganglioneuromas comprise benign, hamartomatous polyps characterized by an overgrowth of nerve ganglion cells, nerve fibers, and supporting cells in the gastrointestinal tract. This polypsis has been divided into 3 subgroups, each with a different degree of ganglioneuroma formation: polypoid ganglioneuroma, ganglioneuromatous polyposis, and diffuse ganglioneuromatosis. The ganglioneuromatous polyposis subgroup is not known to coexist with systemic disorders that often have an associated intestinal polyposis, such as multiple endocrine neoplasia type IIb, neurofibromatosis type I, and Cowden syndrome. We report a case of ganglioneuromatous polyposis plus cutaneous lipomatosis in a 41-year-old man with no established systemic disease. However, he possessed unique anatomic findings in addition to his ganglioneuromatosis, suggesting that the ganglioneuromatosis-lipomatosis in our patient may represent an unrecognized syndrome. This case report and brief review of the literature provide an overview of intestinal ganglioneuromatosis in relation to the hereditary polyposis syndromes and describe the individual ganglioneuromatosis subgroups.

(Arch Pathol Lab Med. 2006;130:1561–1566)

The hereditary polyposis syndromes of the gastrointestinal tract are classified as adenomatous or hamartomatous.1 The adenomatous polyposes include familial adenomatous polyposis (FAP), Gardner syndrome, and Turcot syndrome. These polyposes are benign epithelial neoplasms that have an increased risk of malignant transformation or have a malignant eventuality.2

The hamartomatous polyposes are benign malformations of tissue elements indigenous to the gastrointestinal tract.1 They include intestinal ganglioneuromatosis, juvenile polyposis syndrome, Peutz-Jeghers syndrome, Cowden syndrome, and Ruvalcaba-Myhre-Smith syndrome. Depending on the syndrome, the hamartomatous polyposes have intestinal and extraintestinal neoplastic potential.3 For example, individuals with juvenile polyposis syndrome and Peutz-Jeghers syndrome have established, increased risks for intestinal cancer.4,5

As part of the hamartomatous polyposes, intestinal ganglioneuromatosis is a benign proliferation of nerve ganglion cells, nerve fibers, and supporting cells of the enteric nervous system.1 Common symptoms include constipation, diarrhea, or bleeding. In the gastrointestinal tract, these overgrowths can project into the lumen as polyps, thicken the mucosa, or extend from the serosal surface. The Table categorizes the hereditary polyposis syndromes and highlights the subgroups of intestinal ganglioneuromatosis.

REPORT OF A CASE

A 41-year-old Caucasian man with no personal history of malignancy underwent a colonoscopy because of a family history of colon cancer. The patient reported having 1 to 2 bowel movements per day with intermittent blood in his stool, but he denied abdominal pain, diarrhea, or weight loss. He and his family had no known history of FAP, multiple endocrine neoplasia type IIb (MEN IIb), neurofibromatosis type I (NF1, also known as von Recklinghausen syndrome), or Cowden syndrome. The colonoscopy revealed greater than 100 sessile polyps ranging grossly in size from 1 to 2 mm throughout the entire colon. FAP or attenuated FAP was suspected clinically. Subsequent pathologic examination of the colonoscopic biopsy specimens revealed tubular adenomas in 1 of 5 fragments from the hepatic flexure and 1 of 5 fragments from the descending colon. The remaining 43 colonoscopic biopsy fragments from the hepatic flexure to the sigmoid colon were diagnosed as chronic inflammation, fibrosis, and focal acute inflammation.

As a result of the colonoscopy and suspected adenomatous polyposis, the patient also underwent an esophagogastroduodenoscopy. In the esophagus, white nummular lesions were noted, but no biopsy specimens were obtained. In the stomach, 3 pedunculated and sessile polyps were identified and biopsied. Pathologic examination of the gastric antrum biopsy specimen favored reactive inflamed mucosa. Biopsy specimens from the gastric cardia and duodenum revealed no specific histopathology.

Physical examination revealed an obese man (body mass index of 40). No pigmented skin lesions were identified. Of note, there were multiple, soft, mobile, rubbery masses located in the skin over the abdomen, right elbow, right forearm, anterior lower right leg, and left ankle. Surgical excision and subsequent pathologic examination of the right forearm mass yielded a histologic diagnosis of a lipoma with a benign lymph node. A computed tomography scan of the abdomen did not reveal any intestinal masses; only a possible adrenal myelolipoma was visualized.

The patient was referred to genetic counseling for a suspected familial polyposis. Without genetic testing results, the patient elected to undergo a total abdominal colectomy with ileoproctostomy.
Hereditary Polyposis Syndromes

<table>
<thead>
<tr>
<th>Hamartomatous</th>
<th>Adenomatous</th>
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<tbody>
<tr>
<td>Intestinal ganglioneuromas</td>
<td>Familial adenomatous polyposis</td>
</tr>
<tr>
<td>Polypoid ganglioneuroma</td>
<td>Gardner syndrome</td>
</tr>
<tr>
<td>Ganglioneuromatous polyposis</td>
<td>Turcot syndrome</td>
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<tr>
<td>Diffuse ganglioneuromatosis</td>
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<td>Juvenile polyposis syndrome</td>
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<td></td>
<td>Peutz-Jeghers syndrome</td>
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<td>Ruvalcaba-Myhre-Smith syndrome</td>
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<td>Ruvalcaba-Myhre-Smith syndrome</td>
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PATHOLOGIC FINDINGS

Gross

Gross examination of the colectomy specimen revealed a 148-cm segment of intestine containing 2 cm of small intestine, an ileocecal valve with appendix, and remaining large intestine. On the mucosal surface throughout the large intestine, there were 121 rounded polyps ranging from 0.3 to 0.8 cm in diameter (Figure 1). No ulcerations or other lesions were observed. The polyps were confined to the lumen of the colon, and the serosal surface was unaffected.

Microscopic

Histologic examination of the polyps revealed a hamartomatous collection of nerve ganglion and stromal cells in the lamina propria that ensheathed the overlying glands and formed a nodular configuration (Figure 2, A and B). The glands were elongated, but they did not possess crowded cells with hyperchromatic nuclei typically seen in conventional tubular adenomas. Immunohistochemistry demonstrated that the ganglion cells in the lamina propria were reactive to S100 (Figure 2, C). Additionally, other polyps had an expansion of adipose tissue along or were admixed with stromal elements in the mucosa or submucosa (Figure 2, D).

This case was also reviewed by the Division of Gastrointestinal Pathology at the Armed Forces Institute of Pathology (Washington, DC). No dysplasia or adenomas were identified. The final diagnosis was “Colon: Hamartomatous polyps; ganglioneuromatous, stromal, and lipomatous.”

COMMENT

Shekitka and Sobin6 categorized ganglioneuromas (GNs) of the intestinal tract into 3 groups: polypoid GNs, ganglioneuromatous polyposis, and diffuse ganglioneuromatosis. Polypoid GNs are small, sessile, or pedunculated polyps with a histologic resemblance to hyperplastic polyps, juvenile polyps, or adenomas. In the intestinal tract, these lesions are solitary or few in number. Here, nerve ganglion cells are found in nests in the mucosa and submucosa, usually without significant disarray in the architecture of the surrounding tissues (Figure 3).

In ganglioneuromatous polyposis, there are typically greater than 20 sessile or pedunculated mucosal and/or submucosal lesions.9 There is greater variability in ganglionic, neural, and supportive cell content and demarcation when compared to polypoid GNs (Figures 1 and 2). However, the polyps also may be microscopically indistinguishable from polypoid GNs.

Finally, diffuse ganglioneuromatosis is a disseminated, nodular, intramural or transmural proliferation of neural elements that involves the enteric plexuses.6 These lesions are large (1–17 cm), are poorly demarcated, and can distort the surrounding tissue architecture (Figure 4, A through C). The histology ranges from a hyperplastic expansion of the myenteric plexus to a transmural ganglioneuromatous proliferation. Diffuse ganglioneuromatosis may exist as an isolated finding, or it is often observed as a component of MEN IIb or NF1.

In the present case report, the patient’s intestinal ganglioneuromatosis was confined to the mucosa and most resembled the ganglioneuromatous polyposis subtype. The size and number of polyps in our patient correspond to the description given by Shekitka and Sobin.6 Interestingly, our patient also had multiple cutaneous lipomas, a clinical finding that has been identified previously in patients with ganglioneuromatous polyposis.9

Associated Anatomic Findings

Although the diffuse ganglioneuromatosis subgroup may be linked with syndromes such as MEN IIb or NF1, there are no known associations between the ganglioneuromatous polyposis subgroup and an established systemic disorder.6,9,10 However, there are occasional, coexistent anatomic findings in patients with ganglioneuromatous pol-
Intestinal Ganglioneuromatosis

Figure 2. Ganglioneuromatous polyposis. A, Low-power microscopic view of nerve ganglion and stromal cells in the lamina propria interspersed between the normal glands. Black arrows identify some of the ganglion cells (hematoxylin-eosin, original magnification ×100). B, High-power microscopic view of the ganglion cells in the lamina propria. The black arrow highlights a ganglion cell (hematoxylin-eosin, original magnification ×400). C, The ganglion and surrounding cells demonstrate immunoreactivity to S100 (original magnification ×100). These cells envelop the overlying glands. D, Lipomatous polyp with mucosal and submucosal expansion of adipose tissue (hematoxylin-eosin, original magnification ×20). These microscopic views originate from the colon of the patient in this case report.

yposis. As briefly mentioned earlier, Shekitka and Sobin6 observed multiple cutaneous lipomas and/or skin tags on the extremities or face in a subset of their patients with ganglioneuromatous polyposis. The patient in this case report also shared these cutaneous manifestations on his arms, abdomen, and legs.

Adenomas may be an associated anatomic finding with intestinal ganglioneuromatosis. Michalak et al10 reported few coexisting adenomatous polyps in their patients. Additionally, Rafiq et al11 and Weidner et al12 described adenomatous and juvenile polyps in individuals with intestinal ganglioneuromatosis. Our patient had 2 tubular adenoma fragments from initial precolectomy biopsies, but no more adenomatous tissue was identified after examining 121 polyps from the colectomy specimen. Additionally, no juvenile polyps were present. Therefore, tubular adenomas may be observed in the setting of ganglioneuromatous polyposis; however, the adenomas do not appear to be the predominant feature.

Genetics and Pathophysiology

Although no exact mechanism has been elucidated, a soluble nerve growth factor in patients with intestinal ganglioneuromatosis has been hypothesized to contribute to GN development. DeSchryver-Kecskemeti et al13 suggested the existence of such a factor in an individual with MEN IIb and coexistent intestinal ganglioneuromatosis. Using an in vitro bioassay, they identified a component from their patient’s serum that promoted neurite growth of chick embryo sensory ganglia. This hypothesis of a nerve growth factor dependence in ganglioneuromatosis also has been supported by other investigators.14

The genetic components to various gastrointestinal polyposis syndromes have been identified. The susceptibility genes for several polyposes are as follows: FAP with the adenomatous polyposis coli (APC) gene,15 juvenile polyposis syndrome with the SMAD4 gene,16 Peutz-Jeghers syndrome with the LKB1 gene,17 Cowden syndrome and Ru-
valcaba-Myhre-Smith syndrome with the PTEN gene,\textsuperscript{18} MEN with the RET gene,\textsuperscript{19} and NF1 with the NF1 gene.\textsuperscript{20} Although susceptibility genes have been characterized for many gastrointestinal polyposes, unfortunately, no individual gene or genes have been specifically linked to intestinal ganglioneuromatosis.

It is possible that the development of ganglioneuromatosis may be due to defective tumor suppressor gene signaling. MEN IIb, NF1, and Cowden syndrome all have tumor suppressor gene abnormalities (RET, NF1, PTEN, respectively). Additionally, these tumor suppressor genes all have overlapping signaling via the Akt and mTOR signal transduction pathways.\textsuperscript{18-22} Thus, GN formation in MEN IIb, NF1, and Cowden syndrome may result from inappropriate signaling along the Akt-mTOR pathway. One could speculate that a genetic aberration for intestinal ganglioneuromatosis might also be identified in Akt-mTOR signal transduction.

Despite the available genetic screening for polyposis syndromes,\textsuperscript{23-25} the referral for genetic counseling was not utilized by our patient in the present report. Thus, the genotype of the patient is unknown. Nevertheless, the histologic analysis of the polyps from our patient supports a predominantly hamartomatous, not adenomatous, polyposis. Therefore, an adenomatous polyposis syndrome is unlikely in our patient.

**Intestinal Ganglioneuromatosis and Colon Cancer**

There is a known association between colon cancer and the adenomatous polyposis syndromes.\textsuperscript{2} However, for the hamartomatous polyposis syndromes, only Peutz-Jeghers syndrome\textsuperscript{4} and juvenile polyposis syndrome\textsuperscript{5} have established, increased risks for intestinal malignancy. Despite the recognized connections between colon cancer and the hamartomatous polyposes of Peutz-Jeghers syndrome and juvenile polyposis syndrome, the link between intestinal ganglioneuromatosis and malignancy is not well established. Although investigators have described the coexistence of intestinal ganglioneuromatosis and colorectal adenocarcinoma,\textsuperscript{26,27} the evidence is limited to case reports. Additionally, other reports indicate that no such connec-
tion between colorectal cancer and intestinal ganglioneuromatosis exists.\textsuperscript{1,2,8-20} Finally, in the study by Shekita and Sobin,\textsuperscript{9} none of their patients with intestinal ganglioneuromatosis (follow-up period of 3.3–24 years) developed colo

A Syndrome for Ganglioneuromatous Polyposis?

The prevailing understanding of intestinal ganglioneuromatosis is that only the diffuse ganglioneuromatosis subgroup is associated with systemic disorders, such as MEN II\textsuperscript{b},\textsuperscript{7,13,30-32} NFI\textsuperscript{8,33-35} Cowden syndrome,\textsuperscript{36,37} and Ruvalcaba-Mhyre-Smith syndrome.\textsuperscript{38-40} The clinical features corresponding to these syndromes were absent in our patient. For example, our patient did not have a marfanoid habitus and mucosal neuromas on the lips and tongue (associated with MEN II\textsuperscript{b}),\textsuperscript{31-42} café au lait spots and cutaneous neurofibroma (associated with NFI),\textsuperscript{5,44} trichilemmomas (associated with Cowden syndrome),\textsuperscript{45,46} or macrocephaly and tongue hamartomas (associated with Ruvalcaba-Mhyre-Smith syndrome).\textsuperscript{38-40}

Nevertheless, the ganglioneuromatous polyposis subgroup is associated with various extraintestinal phenomena (ie, lipoma and acrochordon formation), and these anatomic findings in aggregate may represent an under


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