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Original contribution

Morphologic characterization of hamartomatous gastrointestinal polyps in Cowden syndrome, Peutz-Jeghers syndrome, and juvenile polyposis syndrome☆,☆☆

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Summary The morphologic features of the gastrointestinal polyps in hamartomatous polyposis syndromes are poorly defined. Our aim was to better characterize the gastrointestinal hamartomas in these syndromes. A blinded review was performed regarding many histologic features for every polyp. The study included 15 Cowden syndrome, 13 Peutz-Jeghers (PJS), 12 juvenile polyposis (JuvPS) patients, and 32 cases of sporadic hamartomatous polyps. A total of 375 polyps were examined. Cowden syndrome polyps were characteristically colonic, sessile, small, without surface erosion, and showing mildly inflamed fibrotic lamina propria with smooth muscle proliferation and lymphoid follicles. They showed the least degree of cystic glands and had no thick mucin. Uncommon but specific features were ganglion cells and nerve fibers within the lamina propria and mucosal fat. PJS polyps were typically of small or large bowel origin, often exophytic, seldom eroded, with inflamed edematous and fibrotic lamina propria and dilated cystic glands filled with often thick mucin. All PJS polyps showed smooth muscle proliferation, frequently widespread. The polyps of JuvPS were typically colonic, large, exophytic, eroded, with strikingly edematous, fibrotic markedly inflamed lamina propria, cystic glands filled with frequently thick mucin, and the least degree of smooth muscle proliferation. Nonsyndromic hamartomatous polyps were similar to JuvPS polyps; however, they were more often colonic, were

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smaller, showed more widespread smooth muscle proliferation, and were less likely to contain thick mucin. In conclusion, we were able to define the characteristic hamartomatous polyp for each hamartomatous polyposis syndrome. Awareness to these features may aid in the diagnosis of these rare syndromes.

1. Introduction

The hamartomatous polyposis syndromes comprise a diverse group of genetic, clinical, and pathologic entities. The most common and important, due to their increased cancer rates, are Cowden syndrome (CS), Peutz-Jeghers syndrome (PJS), and juvenile polyposis syndrome (JuvPS) [1–5].

CS, an autosomal-dominant condition affecting 1 in 200 000 people, is characterized by multiple hamartomatous lesions [1–7]. Gastrointestinal (GI) polyposis is a common manifestation, can occur throughout the GI tract, and is reported to have a markedly varied histology, with predominantly hamartomatous but also adenomatous, inflammatory, hyperplastic, lipomatous, and ganglioneuromatous polyps [5–7]. Consensus criteria have been established to assist in the diagnosis of CS, which frequently presents with various signs and symptoms [2,8]. CS patients are at particularly high risk for developing cancer of the breast, thyroid, ovary, endometrium, uterine cervix, and urinary bladder [1–5,7]. CS probably also confers a risk of colorectal cancer [6]. Germline mutations in the *PTEN* (phosphatase and tensin homolog) tumor suppressor gene located on chromosome 10q are found in approximately 80% of patients with CS [5,7].

PJS is an autosomal-dominant inherited hamartomatous polyposis syndrome with a prevalence of approximately 1 in 200 000. PJS is characterized by melanotic mucocutaneous hyperpigmentation, which often fades with age, and GI hamartomatous polyps, mostly in the small bowel but also in the colon and stomach [7,9–11]. These hamartomatous polyps can cause abdominal pain and intussusception, sometimes leading to bowel obstruction and severe GI bleeding [10]. PJS is now recognized as a cancer predisposition syndrome, because these patients are at very high relative risk for colorectal cancer and a variety of extracolonic malignancies. The malignancies recognized include breast, pancreas, thyroid, stomach, small intestine, ovary, endometrium, uterine cervix, testis, multiple myeloma, and skin [11–13]. Patients with PJS have a 93% cumulative lifetime risk for cancer [14,15], including an almost 70% risk of GI cancer [2,3]. Germline mutations in the tumor suppressor gene *STK11*/*LKB1* on chromosome 19p are responsible for the PJS [16]. These mutations are found in up to 80% of affected individuals; up to 25% of documented cases are sporadic [7,15].

JuvPS, the most common of the hamartomatous polyposis syndromes, affects 1 in 100 000 and occurs as an autosomal-dominant inherited disorder in approximately 30% of the patients; the remaining cases represent de novo mutation [15,17]. JuvPS is characterized by the presence of multiple hamartomatous polyps affecting the colon and rectum. Unlike sporadic colorectal juvenile polyps, which are relatively common, occurring in up to 2% of children younger than 10 years, the polyps of JuvPS are more numerous and may affect the proximal GI tract polyps [3,5,16]. Patients with JuvPS are at increased risk for colorectal, pancreatic, and upper GI cancer, with an overall risk of GI malignancies at 55% [7,15,18,19]. Both sporadic and inherited forms share similar genetics: germline mutations of *SMAD4* (mothers against decapentaplegic homolog 4, also known as *MADH4* and *DPC4*), located on the chromosome 18q, are detected in approximately 15% of patients with JuvPS. The *BMPR1A* gene (bone morphogenetic protein receptor-type 1A), located on chromosome 10q, is mutated in about 25% of JuvPS patients [15,20,21]. *ENG* germline mutations have been found in JuvPS presenting in early childhood [18]. All 3 genetic changes cause disruption of the transforming growth factor β signal transduction pathway [22].

Pathologists frequently fail to raise the suspicion of a hamartomatous polyposis syndrome based on the GI polyps' morphology. CS polyps are sometimes interpreted as hyperplastic polyps, juvenile polyps, or merely hamartomatous polyps [7,23]. Patients with CS can present with multiple juvenile colonic polyps and therefore be misdiagnosed as having JuvPS [3]. Also, although PJS polyps are thought to demonstrate characteristic histologic features, with "classic" tree branchlike pattern, this arborizing smooth muscle configuration is more pronounced in the small intestine than in the colon, where these polyps may be misdiagnosed as mucosal prolapse polyp [24]. Furthermore, as there are no known histologic differences between sporadic and syndromic juvenile polyps, it is currently not possible to raise the suspicion of JuvPS based on a solitary or even a couple of colorectal juvenile polyps [7].

The genetic bases have been determined in large part for all of these syndromes. However, careful systematic genotype-phenotype analysis specifically of GI polyp morphology has not been done. The prevalence of various morphologic features of these polyps in known genetic backgrounds remains poorly defined. This needs to be rectified because polyp morphology is one of the major factors contributing to correct diagnosis, clinical management, and research study design in these syndromes. Appropriate identification of individuals and families affected with these syndromes is crucial because these