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Peutz-Jeghers syndrome: a critical look at colonic Peutz-Jeghers polyps

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Peutz-Jeghers syndrome is an autosomal dominant condition characterized by gastrointestinal hamartomatous polyps. The pathologic identification of a Peutz-Jeghers polyp is integral to the diagnosis of this syndrome that often remains undiagnosed until after these polyps are identified. Histologically, Peutz-Jeghers polyps are characterized by a distinctive arborization of smooth muscle within the lamina propria. Colonic Peutz-Jeghers polyps, however, may mimic mucosal prolapse polyps or virtually any colonic polyp that undergoes prolapse. In this paper, we explore the morphological features of colonic Peutz-Jeghers polyps and the diagnostic challenges associated with these polyps. Colonic polyps from patients with Peutz-Jeghers syndrome were identified ($n=34$). The control cohort, included mucosal prolapse polyps ($n=5$), hyperplastic polyps ($n=10$) and tubular adenomas with prolapse ($n=9$), ganglioneuromatous polyps ($n=2$) and juvenile polyps ($n=14$). Intramucosal smooth muscle fibers were identified in all classes of polyps. Twenty-three of the 34 colonic Peutz-Jeghers polyps were characterized by lobulated clusters of colonic crypts. On immunohistochemistry, desmin-positive smooth muscle fibers were seen surrounding these lobules. This lobular organization of the crypts was not identified in mucosal prolapse polyps and hyperplastic polyps or tubular adenomas with prolapse; only one of the 14 juvenile polyps showed this pattern of reactivity on a desmin stain. Our data suggests that the histologic hallmark of colonic Peutz-Jeghers polyps is the lobular organization of the crypts, and that an arborizing pattern of smooth muscle proliferation is neither sensitive nor a specific marker of colonic Peutz-Jeghers polyps. The presence of desmin-positive smooth muscle fibers surrounding the lobules is a helpful diagnostic feature of colonic Peutz-Jeghers polyps, and facilitates the distinction of these polyps from non-Peutz-Jeghers polyps with prolapse-like changes.
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Peutz-Jeghers syndrome is an autosomal dominant condition characterized by hamartomatous polyps (Peutz-Jeghers polyps) of the gastrointestinal tract and mucocutaneous freckling. The syndrome is associated with significant morbidity and mortality. One-third of patients are symptomatic by age 10, and half of patients by age 20 have experienced intussusception, obstruction or bleeding. Patients with Peutz-Jeghers syndrome also have an increased risk of malignancy, with an overall lifetime risk of 93%. Although pancreatic carcinoma is one of the most common gastrointestinal malignancies reported, colonic adenocarcinomas are also observed. These patients may also develop extra-intestinal malignancies, including in the breast, ovary, lung, uterine cervix and testis.[1]

The molecular basis for Peutz-Jeghers syndrome is a germline mutation of the serine threonine kinase/liver kinase B1 gene (STK11, formerly known as LKB1) on human chromosome 19p13. Mutations in STK11 have been identified in up to 70% of familial Peutz-Jeghers cases.[2] The frequency of loss of heterozygosity in colonic polyps and adenocarcinomas in Peutz-Jeghers syndrome patients is 25–38% and 64–100%, respectively.[3] However, recent animal studies have shown that biallelic loss of STK11 is not necessary for polyp formation.[4]

WHO criteria for the clinical diagnosis of Peutz-Jeghers syndrome are: (1) detection of three or more histologically confirmed Peutz-Jeghers polyps, or (2) the presence of any number of Peutz-Jeghers polyps in a patient with a family history of the syndrome, or (3) detection of characteristic, prominent

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mucocutaneous pigmentation in a patient with a family history of the syndrome, or (4) detection of any number of Peutz-Jeghers polyps in a patient with prominent mucocutaneous pigmentation.[5]

The pathologic identification of a Peutz-Jeghers polyp is thus integral to the diagnosis of the syndrome, which often remains undiagnosed until these polyps are correctly identified. However, precise classification of a Peutz-Jeghers polyp can be challenging. Peutz-Jeghers polyps of the small intestine show a distinctive arborization of smooth muscle. While Peutz-Jeghers polyps of the stomach and colon also show intramucosal smooth muscle fibers, this distinctive arborization pattern is less prominent, and may be entirely absent.[6] Furthermore, both gastric and colonic Peutz-Jeghers polyps may mimic other polyps with prolapse. In fact, in one study the accuracy of distinguishing gastric Peutz-Jeghers polyps from hyperplastic polyps and juvenile polyposis polyps was reported to be only 18%.[7] Nevertheless, to date, the diagnosis of Peutz-Jeghers syndrome rests significantly on the pathologic recognition of a Peutz-Jeghers polyp.

In this paper, we explore the morphological features of colonic Peutz-Jeghers polyps and the diagnostic challenges associated with these polyps. To the best of our knowledge such a comprehensive evaluation of colonic Peutz-Jeghers polyps has not been previously published.

Materials and methods

Polyps from patients with Peutz-Jeghers syndrome were identified from the surgical pathology files of the Massachusetts General Hospital. The corresponding medical records were reviewed to confirm that the diagnosis of Peutz-Jeghers syndrome met the current WHO criteria. The control cases representing potential mimics of Peutz-Jeghers polyp, included mucosal prolapse polyps, hyperplastic polyps and tubular adenomas with prolapse, ganglioneuromatous polyps and juvenile polyps.

Hematoxylin & eosin (H&E) stained slides were reviewed to confirm the histologic diagnoses. Particular attention was paid to the presence and pattern of distribution of smooth muscle within the lamina propria.

In addition, immunohistochemical evaluation for desmin was performed on all cases (M0760; Dako, USA; Mouse monoclonal antibody; 1:80 dilution) using the avidin–biotin complex (ABC) method.

Results

Clinical Data

Peutz-Jeghers Polyp Cohort. We evaluated 34 colonic Peutz-Jeghers polyps from 11 patients. Mean age at diagnosis was 23, with a male to female ratio of 8:3. The mean size of the polyps was 1.1 cm. All 11 patients met the WHO diagnostic criteria: nine patients had at least three histologically confirmed Peutz-Jeghers polyps, and two patients had at least one characteristic polyp with prominent mucocutaneous freckling. Two patients died of malignancies: one male at age 42 of pulmonary adenocarcinoma, which tested negative for KRAS and EGFR mutations (STK11 testing was not performed) and one female at age 44 of endocervical adenocarcinoma. We also evaluated 12 small intestinal Peutz-Jeghers polyps.

Control Cohort. The control cohort was comprised of colorectal hyperplastic polyps ($n=10$) and adenomatous polyps ($n=9$). Both sets of cases showed an arborizing pattern of smooth muscle proliferation within the lamina propria. Also included in the control group were mucosal prolapse polyps ($n=5$), ganglioneuromatous polyps ($n=2$) and juvenile polyps ($n=14$). Ten of the juvenile polyps were non-syndromic, while four were from individuals with juvenile polyposis syndrome.

Histology

The polyps were composed entirely of colonic-type epithelium. At least a few smooth muscle fibers were identified within all polyps, the majority of which were discontinuous with the muscularis mucosae; however, only 14 (41%) of the polyps showed an arborizing pattern of smooth muscle proliferation. None showed adenomatous transformation.

Notably, in 23 of the 34 polyps (68%) the crypts were organized in a lobular configuration (Figures 1 and 2). These lobules of colonic mucosa were either located within the mucosa ($n=23$) or appeared to extend into the submucosal layer as misplaced epithelium ($n=3$). The larger lobules showed dilated crypts at the center, while smaller crypts were noted at the periphery (Figure 3). The outermost crypts were associated with a few mitotic figures and, when present, Paneth cells. The overall appearance suggest that these lobules maintained some polarity with preservation of the lumen at the center of the lobule (Figure 3). Smooth muscle fibers were visualized, at least focally around the lobules in 13 cases (38%) (Figure 1). Stromal hemosiderin deposits were identified in one case.

In nine cases, this lobular configuration was not visualized on the H&E, although it became clearly visible on a desmin immunohistochemical stain in six cases (see below).

Desmin Immunohistochemical Stain. In 29 of the 34 cases (85%), a delicate framework of desmin-positive fibers surrounded the lobule (Figures 1 and 2). In most cases, the smooth muscle fibers entirely surrounded the lobules of colonic mucosa, however,

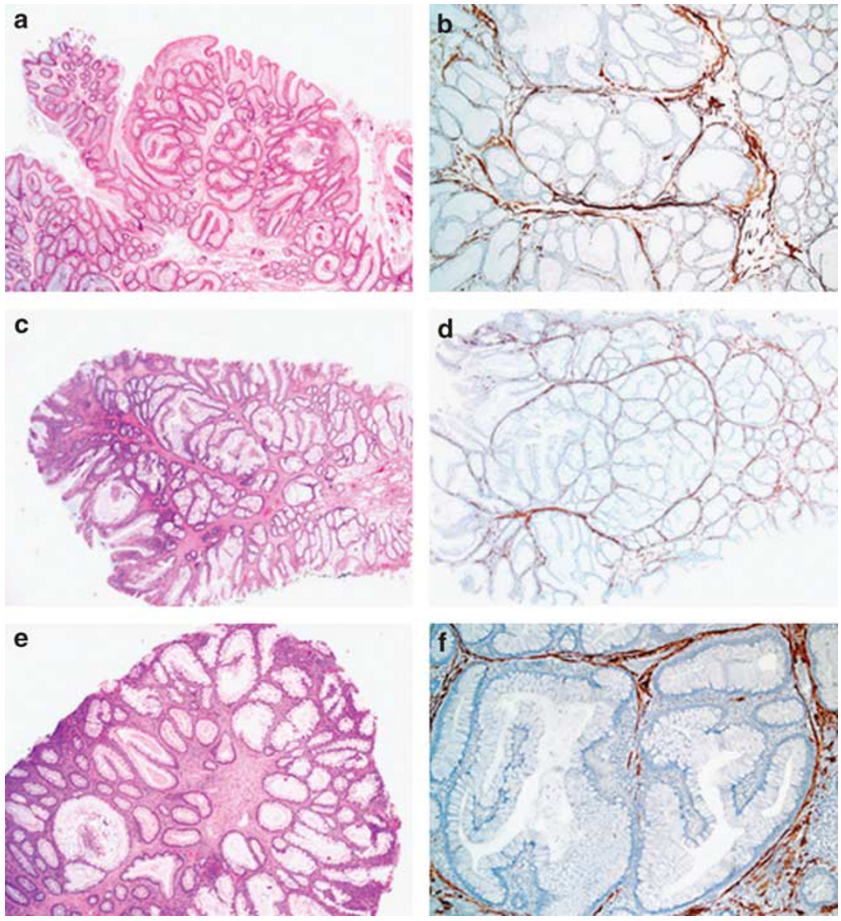

Figure 1 Peutz-Jeghers polyps. Low-power view of a Peutz-Jeghers polyp demonstrating the lobular pattern of organization of the crypts (**a**). A desmin immunostain shows well-circumscribed aggregates of crypts surrounded by smooth muscle fibers (**b**). Another Peutz-Jeghers polyp with a lobulated pattern of organization of the crypts (**c**) and the corresponding immunohistochemical stain for desmin (**d**). The lobular pattern in this Peutz-Jeghers polyp is less distinct (**e**). However, a desmin stain uncovers the lobular pattern (**f**).

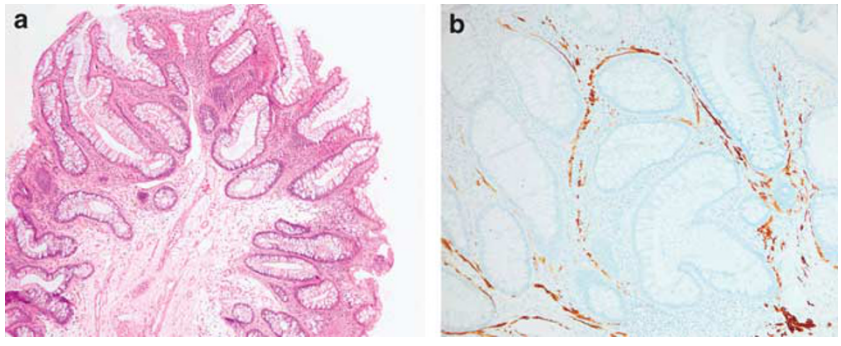

Figure 2 This Peutz-Jeghers polyp measured 6 mm in diameter. A nodular pattern is appreciable on low power (**a**). One of these lobular units is surrounded by desmin-positive smooth muscle fibers (**b**).

some of the lobules were only partially encircled. The smooth muscle fibers highlighted by the desmin stain were not contiguous with the muscularis mucosae and appeared to arise *de novo*.

An arborizing pattern was also observed in 21 cases, although this pattern was prominent in only five cases. In fact, in polyps measuring <1 cm in greatest dimension, the lobular configuration was the dominant pattern of desmin staining (52%), whereas the arborizing and mixed (arborizing and lobular) patterns were more common in polyps >1 cm (38% each).

Comparison of polyps from patients who met the WHO diagnostic criteria of having more than three Peutz-Jeghers polyps with those who had prominent mucocutaneous freckling with at least one Peutz-Jeghers polyp showed no differences in polyp size and pattern of desmin staining.

Control Cases. We evaluated 40 colonic polyps, including 10 hyperplastic polyps with histological evidence of prolapse, 9 tubular adenomas with histological features of prolapse and 5 mucosal prolapse polyps. We also evaluated 2 ganglioneuromatous polyps and 14 juvenile polyps. Intramucosal smooth muscle fibers were seen in all cases. All cases of hyperplastic, adenomatous and prolapse polyps showed arborizing smooth muscle fibers located between colonic crypts (Figures 4 and 5). In these polyps, the desmin immunostain accentuated the detection of the splayed smooth muscle fibers. However, a lobular pattern of reactivity, as seen in the Peutz-Jeghers polyps, was not seen in any of these cases. Relative to these polyps, juvenile polyps showed a paucity of smooth muscle fibers. Only a single juvenile polyp showed a subtle lobular pattern with smooth muscle fibers identified at the periphery of the lobule, mimicking the pattern seen in Peutz-Jeghers polyps. A ganglioneuromatous polyp lacked the Peutz-Jeghers-pattern of on a desmin immunostain.

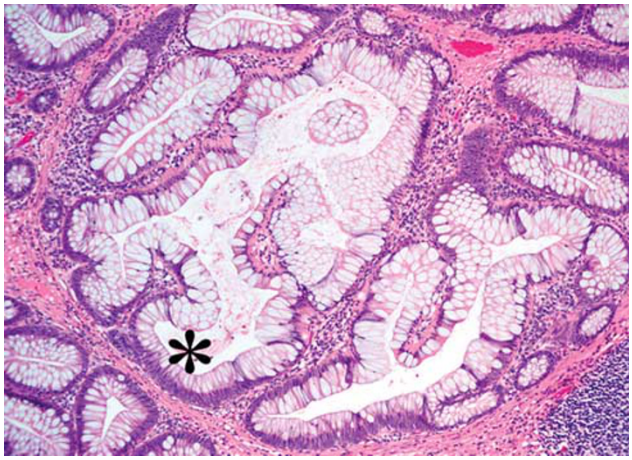

Figure 3 A high-power view illustrates maturation of the epithelium from the base (*) of the crypts to the surface ie, the central portion of the lobules.

Small Intestinal Polyps. All 12 small intestinal Peutz-Jeghers polyp examined, showed the characteristic 'tree branching' pattern of arborization. In addition, a lobular pattern of organization of the crypts was evident in six cases. In sharp contrast to the colonic Peutz-Jeghers polyps, a lobulated pattern of desmin reactivity was noted in only two cases.

Discussion

To the best of our knowledge, this is the only study that critically evaluates the morphological features of colonic Peutz-Jeghers polyps. The histologic hallmark of Peutz-Jeghers polyps is the presence of smooth muscle fibers in an arborizing pattern, and it is often assumed that this is a reliable indicator of Peutz-Jeghers polyps and Peutz-Jeghers syndrome throughout the gastrointestinal tract. However, as this study shows, this appearance is seen in only a minority of colonic Peutz-Jeghers polyps (41%). Furthermore, as virtually all colonic polyps—of all types—are prone to prolapse, the presence of smooth muscle fibers within the lamina propria must be considered a nonspecific feature and cannot

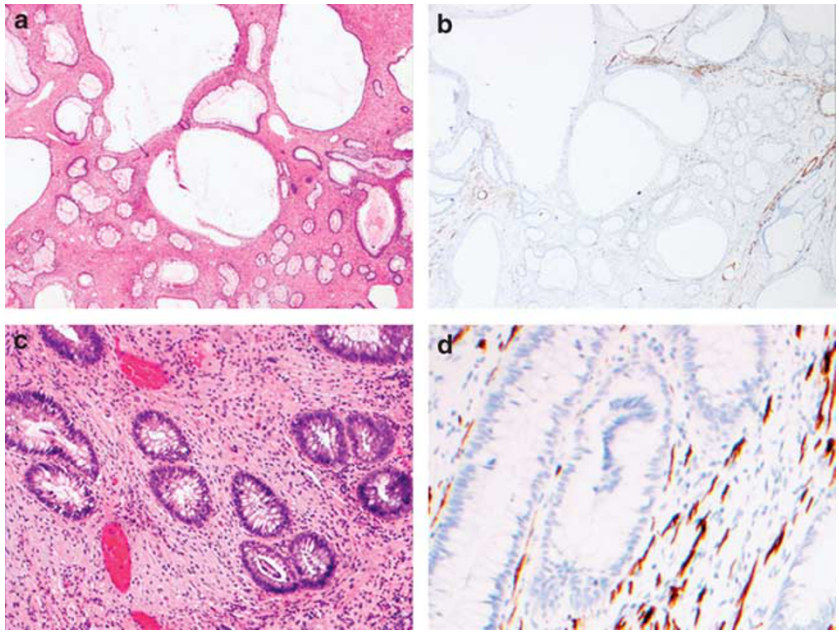

Figure 4 A vaguely lobular pattern of organization of the crypts may be identified in juvenile polyps (**a**). However, the smooth muscle fibers identified do not surround the lobule (**b**). A ganglioneuromatous polyp (**c**) with randomly arranged muscle on a desmin stain (**d**).

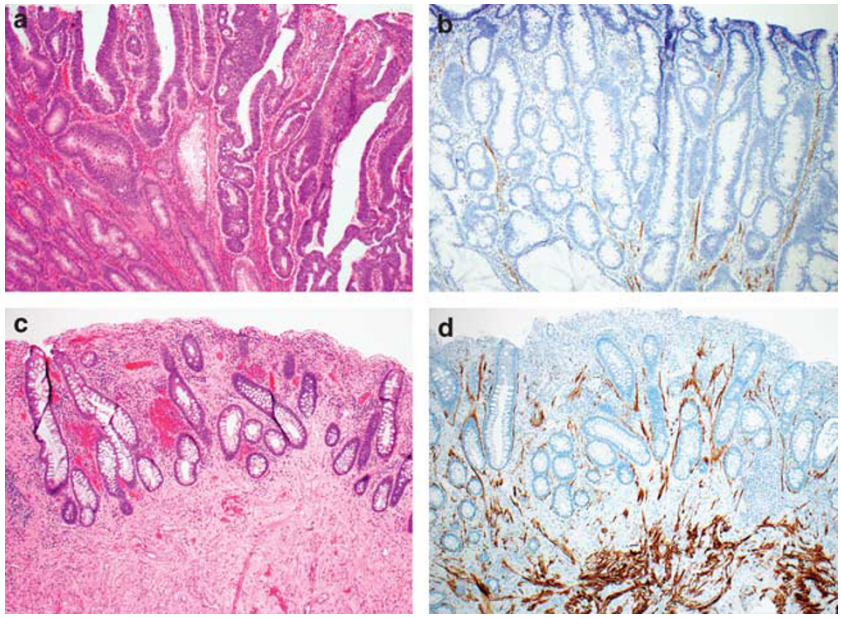

Figure 5 Tubular adenoma (**a**) and mucosal prolapse polyp (**c**), with the corresponding desmin immunostains (**b** and **d**).

be used as a diagnostic criterion. Instead, the hallmark of a colonic Peutz-Jeghers polyp is the lobular organization of colonic crypts, a feature that was identified in the majority of our cases (68%). Interestingly, these lobules appear to be invaginations of the mucosa with the crypt base identified at the periphery of the lobule. While this lobular organization was evident on H&E stained sections in the majority of cases, in 18% of cases a desmin stain was required to uncover this pattern. Altogether, 14% of cases entirely lacked a lobular growth pattern. The only prior study that examined the presence of desmin- and smooth muscle actin-positive fibers in small bowel Peutz-Jeghers polyps reported a arborizing pattern of smooth muscle proliferation.[8] Interestingly, in our study a lobular pattern of organization as highlighted by desmin immunostain was seen in only a minority of small intestinal Peutz-Jeghers polyps (2 of 12).

The significance of identifying a Peutz-Jeghers polyp cannot be underestimated and the implications for both the patient and their family are significant. The patient and their family are at an increased risk of developing carcinoma of the pancreas, stomach, large bowel, breast, ovaries and testis. Importantly, the diagnosis of Peutz-Jeghers syndrome rests primarily on the histological identification of the polyps, and while sequencing for a germline mutation in STK11 may provide irrefutable evidence, such mutations are not demonstrable in 10% of affected individuals.[1] In fact, in the absence of a family history or mucocutaneous pigmentation, the diagnosis is dependent on documenting three diagnostic polyps.

Clinically, the presenting complaints of Peutz-Jeghers syndrome are intestinal obstruction (43%), abdominal pain (23%), blood in the stool (14%) and anal extrusion of polyp (7%).[7] The remaining 13% of cases are diagnosed because of prominent mucocutaneous melanin pigmentation. One of the most frequent forms of presentation in the first decade is intussusception. It could thus be argued that as the vast majority of patients present with small bowel polyps, the diagnostic value of colonic Peutz-Jeghers syndrome is somewhat limited. However, not all patients show small bowel Peutz-Jeghers polyps. In individuals with Peutz-Jeghers syndrome, the topographic distribution and frequency of polyps is as follows: small intestine (64%), colon (53%), stomach (49%) and rectum (32%).[7] Therefore, the enhanced recognition of the diagnostic features of colonic Peutz-Jeghers provides a far easier means to reach a definitive diagnosis of the syndrome.

As the majority of these patients present in the first three decades of life, the main differential diagnosis is between a Peutz-Jeghers polyp and other hamartomatous polyps, particularly juvenile polyps. Juvenile polyps typically lack a lobulated pattern of growth, although occasional polyps may show vague lobulation. However, unlike Peutz-Jeghers polyps, in which the crypts are closely packed, juvenile polyps show abundant stroma between the crypts. In general, the density of the smooth muscle fibers seen in juvenile polyps is generally less than that seen in Peutz-Jeghers polyps. In addition, in our hands, the juvenile polyps showed a haphazard or arborizing pattern of desmin-positive smooth muscle fibers. However, one juvenile polyp did show a vaguely lobulated pattern of desmin immunoreactivity.

Non-hamartomatous polyps are uncommon in the first three decades of life. Nonetheless, one may

occasionally encounter such a polyp in children and young adults, and thus a colonic mucosal polyp with intramucosal smooth muscle fibers does raise a broad differential diagnosis. We therefore examined a series of such polyps to evaluate the specificity of the desmin immunostain. Mucosal prolapse polyps are characterized by the presence of arborizing smooth muscle cells that appear to arise from the muscularis mucosae. None of the mucosal prolapse polyps showed a lobular growth pattern on an H&E nor were there desmin-positive smooth muscle cells surrounding lobular aggregates of crypts. Tubular adenomas and hyperplastic polyps with prolapse-like changes also lack the lobular Peutz-Jeghers polyp-type of immunoreactivity.

Peutz-Jeghers polyps generally do not show foci of hemorrhage or hemosiderin deposition, features commonly associated with other polyps with misplaced epithelium. This suggests that the mechanism of displacement of the epithelium in Peutz-Jeghers polyps differs from misplaced epithelium in other colonic polyps. The 'pseudoinvasion' seen in other colonic polyps is believed to be secondary to twisting of the polyp followed by protrusion of the glands through the muscularis mucosa.[9] The misplaced crypts observed in Peutz-Jeghers polyps appear to be an innate property of this hamartomatous polyp. In fact, as STK11 is a key component of the apparatus that induces cell polarity it has been postulated that perturbation of this gene leads to the florid epithelial misplacement that is characteristic of these polyps.[10]

In conclusion, the mere presence of an arborizing pattern of smooth muscle fibers detected either on an H&E stain or by immunohistochemistry does not distinguish colonic Peutz-Jeghers polyp from its mimics. Indeed, arborizing bundles of smooth muscle fibers may be identified in juvenile polyps, tubular adenomas, mucosal prolapse polyps and hyperplastic polyps. Our data shows that Peutz-Jeghers polyps show a lobulated growth pattern that is generally fairly noticeable on an H&E stain but accentuated on desmin immunostain, and offers a pattern that can be a valuable adjunct to the diagnosis.

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Disclosure/conflict of interest

The authors declare no conflict of interest.

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