Benign Gastrointestinal Mesenchymal BUMPS
A Brief Review of Some Spindle Cell Polyps With Published Names

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• Context.—There are several benign, predominantly spindle cell, mesenchymal proliferations involving the mucosa and/or submucosa in the gut, which present as polyps and pathologists see as polypectomy specimens. These include perineuriomas, Schwann cell nodules, ganglioneuromas, leiomyomas of the muscularis mucosae, inflammatory fibroid polyps, and granular cell tumors.

Objectives.—To evaluate these mesenchymal polyps for their morphologic, immunohistochemical, ultrastructural, and molecular characteristics and to determine some of their associations.

Benign mesenchymal polyps of the gastrointestinal (GI) tract are a group of unusual and interesting lesions. There has been great progress recently in their categorization, including more detailed analysis of their light microscopic features as well as their immunohistochemical and molecular characteristics. The field has changed dramatically during the past 10 years, when, in 2001, new legislation modified Medicare, which then began reimbursement for screening colonoscopy in patients at average risk for colorectal carcinoma.1 This has led to more of all types of polyps being identified, including benign mesenchymal polyps, particularly in the colon. These benign mesenchymal polyps of the colon present as small, asymptomatic, and usually solitary polyps. However, pathologists may find them difficult to diagnose, partly because of their rarity, partly because several have been described only relatively recently, and partly because some have similar and overlapping histologic features.

This review covers several benign mesenchymal polyps of the GI tract composed predominantly of spindle cells and includes the newest data regarding their histologic, immunohistochemical, ultrastructural, and molecular characteristics. Because they all are small, superficial proliferations found by accident as endoscopic polyps and because the age and sex of the patients essentially mirror the age and sex of individuals who have endoscopic procedures for various reasons, discussion of their clinical features is limited to features that are specific for each polyp type. Similarly, all the polyps are the differential diagnosis for each other, so we will not belabor the differential diagnosis issue. Distinctive names have been given to several such polyps, but in practice, we still see many mesenchymal polyps that are, as yet, unnamed. In our institution, we diagnose these unnamed mesenchymal polyps simply as benign unclassified mucosal polyps or BUMPs. Almost all of these small polyps occur in the mucosa and submucosa of the gastrointestinal tract only, yet in many publications, gastrointestinal stromal tumors are included in the differential diagnosis. Gastrointestinal stromal tumors are mural tumors that only involve the mucosa when they are large and malignant and invade into the mucosa. They should not really be part of the differential diagnosis of these benign mesenchymal polyps.

PERINEURIOMA, FORMERLY KNOWN AS BENIGN FIBROBLASTIC POLYP

Background

This lesion was first described in 2004 by Eslami-Varzaneh et al,2 who gave it the name benign fibroblastic polyp. In 2005, Hornick and Fletcher3 described a series of cases with identical clinical and pathologic findings. However, their study included ultrastructural and immunohistochemical analyses, and they found these tumors had features of perineurial cells, so they designated these lesions intestinal perineuriomas. During the past several years, there has been agreement that benign fibroblastic polyps and intestinal perineuriomas are the same lesion.

Specific Clinical Features

There are none.

Histologic Features

Intestinal perineuriomas are proliferations of plump, uniform spindle cells with pale cytoplasm, indistinct cell borders, and bland nuclei without mitoses. The tumor cells

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fill the lamina propria and spread apart the colonic crypts (Figure 1, A and B). They commonly disrupt the muscularis mucosae and extend into the superficial submucosa (Figure 1, C and D). There is usually a thin, compressed layer of lamina propria between the tumor and the surface epithelium (Figure 2, A). In two-thirds of the cases, the trapped crypts have serrated architecture, so they have an appearance identical to the crypts in a hyperplastic polyp (Figure 2, B).

Ancillary Studies

These tumors express perineurial markers, including epithelial membrane antigen (EMA), GLUT-1, claudin-1, and vimentin (Figure 2, D), and do not express keratins; muscle markers, including actin and desmin; CD34; or neural markers, including S100. Part of the initial confusion regarding this lesion was that in the first 2 studies, vimentin findings were strongly positive and EMA findings were negative, suggesting fibroblastic differentiation. By using higher concentrations of the EMA antibody and enhanced antigen retrieval methods, the polyps from the original studies show positive staining with EMA in a faint, membranous pattern. Ultrastructurally, intestinal perineuriomas are spindled cells with bipolar cytoplasmic processes, and have pinocytic vesicles, identical to perineuriomas found elsewhere in the body.

A recent study confirmed that the serrated epithelium often has BRAF mutations, which hyperplastic polyps frequently harbor, so this truly is a mixed epithelial-stromal polyp, a hybrid hyperplastic polyp/perineurioma. It is not known whether the epithelial changes induce the stromal changes or if it is the other way around.

SCHWANN CELL HAMARTOMA

Background

We have seen small polyps composed of Schwann cells in the lamina propria, which we have been calling mucosal neuromas for lack of a better name and because they had not been reported in the literature, to our knowledge. We assumed that they were like mucosal ganglioneuromas but lacked the ganglion cells. The necessary name and literature was supplied in 2009 by Gibson and Hornick, who called them Schwann cell hamartomas in an attempt to differentiate Schwann cell proliferations with no
association to genetic syndromes from those that are associated with hereditary cancer syndromes, specifically neurofibromatosis type 1 (NF1) and multiple endocrine neoplasia 2B (RET).

Specific Clinical Features

One bit of proof that Schwann cell hamartomas are not syndrome-related is that, with limited follow-up data, there have been no patients with multiple Schwann cell hamartomas, none have recurred, and there have been no reports of malignant behavior.

Histologic Features

These tumors are poorly circumscribed, short fascicles of uniform spindle cells replacing the colonic lamina propria, especially the superficial lamina propria, and separating and entrapping the crypts (Figure 3, A and B). The nuclei are bland and mostly uniform, but occasional larger nuclei are found. The cytoplasmic borders are indistinct. As far as we can tell, these tumors involve the mucosa but never the submucosa.

Ancillary Studies

Schwann cell hamartomas express S100 protein in a strong, diffuse pattern with both nuclear and cytoplasmic staining (Figure 3, C), and some of these lesions have rare axons that stain with neurofilament protein. Immunostains for EMA, CD34, keratins, glial fibrillary acidic protein, claudin-1, smooth muscle actin, and c-kit are negative.

Differential Diagnosis

Perhaps neurofibroma falls into the differential diagnosis, but neurofibromas virtually never occur in the mucosa, unless they are part of a large mural tumor. However, there may be another small, polypoid tumor composed purely of Schwann cells that may or may not be related. In 2005, Lewin et al\textsuperscript{11} published a study of 6 benign Schwann cell tumors with spindled and epithelioid tumor cells that presented as small colonic polyps, which they called benign epithelioid peripheral nerve sheath tumors. These tumors involve not only the colonic mucosa but also have a substantial submucosal component. In fact, one tumor was entirely submucosal. The epithelioid cells have small, bland nuclei; prominent, pale nuclear pseudoinclusions; and abundant eosinophilic cytoplasm, and they stain diffusely with S100. The cells are arranged in whorls. Whether they are related to the Schwann cell hamartomas is not clear, but their submucosal component is certainly different. Perhaps they are a variant.

![Figure 2. Perineurioma. A, The lamina propria is condensed and pushed up just below the surface epithelium. B, Serrated crypts identical to those seen in hyperplastic polyps are trapped within the tumor. C, Faint whirling architecture around the crypts. D, The tumor cells are diffusely positive for vimentin by immunohistochemistry (hematoxylin-eosin, original magnifications ×100 [A and B] and ×200 [C]; original magnification ×40 [D]).](image_url)
Figure 3. Schwann cell hamartoma. A and B, Fascicles of spindled cells replacing the mid and superficial lamina propria, separating the crypts. C, The spindled cells are diffusely positive for S100 protein by immunohistochemistry (hematoxylin-eosin, original magnifications ×100 [A] and ×200 [B]; original magnification ×200 [C]).

Figure 4. Ganglioneuroma. A through C, The mixture of spindled cells and ganglion cells replaces much of the lamina propria and separates the crypts (hematoxylin-eosin, original magnifications ×40 [A], ×100 [B], and ×200 [C]).
GANGLIONEUROMA

Background

Gastrointestinal tract mucosal ganglioneuromas are benign tumors composed of Schwann and ganglion cells. They are usually sporadic and solitary; however, they also occur in a genetic polyposis syndrome, specifically multiple endocrine neoplasia type 2B (RET), neurofibromatosis type 1 (NF1), and familial adenomatous polyposis, and in these syndromes, they are likely to be multiple.

Specific Clinical Features

As mentioned above, most of these polyps are sporadic. Syndromic ganglioneuromas are usually found in younger patients, and the patients are likely to have the signs and symptoms of the syndromes, including family history, diarrhea, constipation, and abdominal pain, but the polyps are asymptomatic. In one study, ganglioneuromas were separated into 3 types, a solitary type and a multiple mucosal type, neither associated with syndromes, and a diffuse type that involved the bowel wall rather than solely the mucosa; it is this latter type that was associated with a syndrome.

Histologic Features

Mucosal ganglioneuromas are proliferations of spindled cells with admixed plump ganglion cells that separate the colonic crypts. There is a layer of lamina propria just under the surface of the mucosa, and the overlying epithelium is typically intact, although sometimes the crypts can have a serrated architecture. The sporadic polyps sometimes resemble juvenile polyps with round contours and many cystic crypts separated by the ganglion and Schwann cells (Figure 4, A through C).

Ancillary Studies

The spindled cells are Schwann cells and stain strongly and diffusely with S100, with a nuclear and cytoplasmic distribution. The ganglion cells stain positively with synaptophysin, neurofilament protein, and neuron-specific enolase.

GRANULAR CELL TUMOR

Background

Granular cell tumors (GCTs) are benign tumors that are thought to be derived from Schwann cells. The GCTs are...
usually found in the skin and oral cavity, especially the tongue, but they occur throughout the GI tract where they are much less common.

Specific Clinical Features

The GCTs of the GI tract are predominantly solitary and are located mostly in the esophagus and right colon, although they occur throughout the GI tract. Multiplicity is exceedingly rare. Occasionally, they can recur, if they were not completely excised.

Histologic Features

The GCTs are composed of plump, polygonal cells with small, uniform nuclei and abundant, eosinophilic, granular cytoplasm. The cells are arranged in nests and sheets with intervening fibrous septae. In the colon, they are mainly found in the submucosa, commonly extending from the submucosa into the base of the mucosa (Figure 5, A through C). In contrast, in the esophagus, they are situated mainly in the lamina propria, abutting the squamous epithelium, which may have the features of pseudoepitheliomatous hyperplasia, a squamous cell carcinoma mimic. This can be a diagnostic problem if only the mucosa overlying the GCT is biopsied. In the colon, there may be regenerative epithelial changes in the mucosa, possibly the result of prolapse caused by the mass, and that can mimic an adenoma.

The edges of the tumor can be either infiltrating or circumscribed, and there is sometimes a peritumoral lymphoid cuff. Hyalinization or calcification or both sometimes occurs. Rarely, nuclear pleomorphism is prominent. The soft tissue counterpart of this tumor has a 3-tiered grading system—benign, atypical, and malignant—based on the presence of necrosis, nuclear atypia, and mitotic activity; however, it is unclear whether the criteria are useful in GCTs of the GI tract.\textsuperscript{14–17}

Ancillary Studies

The cells of GCT are diffusely positive for S100 protein, within both the nuclei and cytoplasm (Figure 5, D). The cytoplasmic granules are positive for periodic acid–Schiff and diastase-resistant. The GCTs also stain positive with the $\alpha$ subunit of inhibin, calretinin, myelin basic protein, and Leu-7 (CD57), supporting Schwann cell derivation of the tumor cells.

Figure 6. Leiomyoma. A through C, Eosinophilic, spindled cell proliferation, which merges with the muscularis mucosae and extends into the base of the mucosa. D, Large, hypertrophic smooth muscle cells, many of which have cytoplasmic, eosinophilic globules (hematoxylin-eosin, original magnifications ×20 [A], ×100 [B and C], and ×400 [D]).
LEIOMYOMA

Background

Polypoid colonic leiomyomas are relatively common. In our anecdotal experience, they are the second most common colonic mesenchymal polyp, behind lipomas.

Specific Clinical Features

In the colon, leiomyomas, also known as leiomyomatous polyps, are small polyps mostly found in the rectum and sigmoid colon and are remarkably unusual elsewhere. We have no explanation for this distribution. In the esophagus, minute leiomyomas, sometimes referred to as seedling leiomyomas, occur mainly in the muscularis propria but are occasionally found in the muscularis mucosae; even there, however, they are so small that they are rarely seen endoscopically as tiny polyps. Elsewhere in the gut, leiomyomas are rare, large mural tumors. There is a male predominance (2.5:1) in all locations.

Histologic Features

Colonic polypoid leiomyomas are circumscribed, nodular proliferations of smooth cells that are in continuity with the fibers of the muscularis mucosae, suggesting that they arise from there. Small fascicles of cells may extend into the base of the overlying colonic mucosa, which is otherwise healthy (Figure 6, A through C). The muscle cells are uniform spindled cells with such abundant fibrillar red to pink cytoplasm that they appear to be hypertrophic compared with the typical leiomyoma cells of uterine leiomyomas, which are generally smaller than healthy smooth muscle cells. The cells often have cytoplasmic, eosinophilic globules, which are actually bundles of smooth muscle filaments (Figure 6, D). The cells have uniform, elongated nuclei with blunt ends. There have been rare examples of leiomyomas with extensive nuclear atypia, and those tumors usually have thick, hyalinized vessels and other degenerative changes. Those tumors have been called symplastic leiomyomas, and they should not be confused with leiomyosarcomas.

Ancillary Studies

Leiomyomas express smooth muscle markers, including actin and desmin. They do not express EMA or neural markers, including S100 protein, keratins, CD34, or other neural markers. Ultrastructurally, leiomyomas have abundant, intermediate filaments, typical of muscle cells. By light microscopy, the cells of leiomyomas, with all that

Figure 7. Gastric inflammatory fibroid polyp. A, Gross view: the proliferation is mostly in the submucosa, and it has a sharp, lower border. B and C, Low-power and high-power views of submucosal spindle cell proliferation with stellate cells, inflammatory cells, and numerous capillaries. (Note the sharp, lower border in B). D, Smooth muscle actin immunohistochemical stain showing the completely disrupted and probably expanded muscularis mucosae as the tumor traverses it (hematoxylin-eosin, original magnifications ×40 [B] and ×400 [C]; original magnification ×40 [D]).
red fibrillar cytoplasm, look so much like smooth muscle cells and so little like any other cell that any kind of immunostaining is likely to be unnecessary.

INFLAMMATORY FIBROID POLyps

Background

Inflammatory fibroid polyps (IFPs) were originally described in 1949 by Vanek under the name *gastric submucosal granulomas with eosinophilic infiltration*, which was simplified to *Vanek tumors*, a term that persists in the clinical literature. They were originally believed to be reparative processes, hence, the designation inflammatory; however, recent molecular studies have called that into question. They were given their current name in 1953 by Helwig and Rainer.

Specific Clinical Features

The IFPs, which are uncommon lesions, are most often found in the stomach, with the terminal ileum as the second site, whereas they are extremely rare in the esophagus and colon. In the stomach, they tend to appear as small, sessile endoscopic polyps, rarely more than 1.5 cm across, and mostly in the pylorus or distal-most antrum. Because they are so small, they rarely produce symptoms, but the larger ones may obstruct the pyloric sphincter and cause symptoms, such as vomiting and pain. In the ileum, where they are much larger than they are in the stomach, they are usually the leading edges of intussusceptions, resulting in intestinal obstruction and all its associated symptoms. Here, they do not present as endoscopic polyps.

Histologic Features

The IFPs have different appearances in different parts of the gastrointestinal tract. For some strange reason or reasons, the gastric and colonic IFPs share histologic features, as do the ileal and esophageal IFPs.

Gastric IFPs, which are mesenchymal polyps, seem to begin at the base of the lamina propria, extending through and disrupting the muscularis mucosa. They have a sharp, well-circumscribed, lower border in the submucosa (Figure 7, A). They are composed of haphazardly arranged stellate and spindled cells, within an edematous stroma with many fine collagen fibers, sometimes referred to as a tissue culture appearance (Figure 7, B through D). There are numerous small blood vessels and many inflammatory cells, including numerous eosinophils and lymphocytes with scattered plasma and mast cells. The gastric tumors have less stromal edema and, therefore, appear more solid compared with the ileal tumors. Gastric IFPs also typically have a prominent perivascular orientation of the various cells. Eosinophils are more prominent than they are in the ileal tumors.

For the sake of completeness, the ileal IFPs, which are really not germane to this review, are discussed anyway. They are intramural proliferations that push against the muscularis mucosa, eventually disrupting it and extending into the mucosa, often ulcerating. They obliterate the submucosa and muscularis propria and often invade the mesentery.

Ancillary Studies

The stellate cells always stain for vimentin and usually for CD34, whereas some of the cells also have dendritic

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**Figure 8.** Benign unclassified mesenchymal polyp. A and B, Proliferation of spindled cells and other components predominantly in the submucosa with a lymphoid aggregate in the middle. C, The proliferation has abundant collagen as well as smooth muscle bundles and blood vessels. This polyp has no name, but it deserves one (hematoxylin-eosin, original magnifications ×40 [A] and ×100 [B]; trichrome stain, original magnification ×100 [C]).
cell and macrophage markers. It seems to be the consensus that the cells are fibroblasts and myofibroblasts, sometimes with unusual markers.2,3

Recent molecular and immunohistochemical research24,25 has shown that many gastrointestinal IFPs harbor activating mutations in the platelet-derived growth factor receptor alpha (PDGFRα) gene, which is also mutated in a subset of gastrointestinal stromal tumors, typically the gastric benign epithelioid variant that do not have a c-kit mutation. In one study, 57 of 60 ileal IFPs (95%) overexpressed PDGFRα by immunohistochemistry, and 33 (55%) had mutations of that gene, whereas the mutation was found in 14 of 19 gastric IFPs (74%) in another study. For many years, these tumors were thought to be reactive; however, the evidence now suggests that IFPs are PDGFRα-driven benign neoplasms. It will be interesting to see whether the name of this tumor is changed, yet again, given this new data.

Differential Diagnosis

Polypoid, small, gastric IFPs have a unique histologic appearance because they are tumors that involve the base of the mucosa and superficial submucosa and contain bland-appearing stellate and spindle cells, haphazardly arranged in an edematous stroma with fine collagen fibers, numerous small blood vessels, and inflammatory cells, including prominent eosinophils. There are no other mesenchymal polyps with this appearance.

BENIGN UNCLASSIFIED MESENCHYMAL POLYPS (BUMPS)

Background

The BUMP’s may be the most common mesenchymal polyps we encounter in our clinical practice. This is a “wastebasket” designation, which probably only exists at our institution because all of the benign polyps have not yet been given names in the literature. As more of these are seen and people write about them, it is likely that many of these polyps will be given proper names and no longer fit in the BUMP category. The perineurioma and Schwann cell hamartoma used to be in this category before they were rescued from oblivion.

Specific Clinical Findings

None.

Histologic Findings

The histology of these polyps is highly varied, likely because these are really many different types of proliferations. They can have spindled cells of various types, adipocytes, blood vessels of all shapes and sizes, and any type of stroma, including collagenous, elastic, and myxoid (Figure 8, A through C).

Ancillary Studies

The BUMP’s will stain positively for markers specific for the types of cells that make up their composition.

References


