Benign Fibroblastic Polyps of the Colon

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Benign fibroblastic polyps of the colon are a recently described entity among mucosal polyps found in the colorectum. These polyps are typically discovered on routine screening colonoscopy within the distal colon. Benign fibroblastic polyps occur most commonly in adult women in the sixth decade of life. Histologically, benign fibroblastic polyps are bland spindle cell lesions that fill the lamina propria and displace the surrounding crypts. The spindle cell proliferation lacks atypia and significant mitotic activity. Hyperplastic changes are frequently present both in the adjacent epithelium and within the lesions. Immunohistochemically, the cells of benign fibroblastic polyps are invariably positive for vimentin with rare focal positivity for CD34 and smooth muscle actin. They are negative for CD117 and S100 protein. Ultrastructurally, benign fibroblastic polyps have features of fibroblastic differentiation. These polyps are benign with no reports, to our knowledge, of recurrence or metastasis.

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Benign fibroblastic polyps of the colon are mucosal spindle cell proliferations first described by Eslami-Varzaneh et al in 2004. The pathogenesis of these lesions is unknown. Theories include an origin from dendritic interstitial cells, follicular dendritic cells, an early stage of inflammatory fibroid polyp, or the result of local inflammation resulting in the formation of scar tissue.1–5 Benign fibroblastic polyps are frequently associated with hyperplastic changes in the surrounding epithelium and within the lesions themselves.1–5 This finding may be due to a currently undetermined epithelial-mesenchymal interaction.1–4 The spindle cells have been shown to have immunohistochemical and ultrastructural findings indicative of fibroblastic differentiation.1–3–4 Regardless of the pathogenesis and differentiation, benign fibroblastic polyps are probably more frequent than the current incidence suggests, and increased awareness among pathologists is likely to result in increased recognition of these polyps.1–3–4

CLINICAL FEATURES

Benign fibroblastic polyps are rare lesions with an estimated incidence of 0.1% to 1.46% of all colonic polyps in different series.1–3 Benign fibroblastic polyps most commonly present as solitary mucosal polyps in asymptomatic patients undergoing routine screening colonoscopy.1–4 Rarely, they have been associated with rectal bleeding and clinical diagnoses of colitis and dyspepsia.2,4 Associated findings have included adenomatous and hyperplastic polyps at different sites, diverticulosis, internal hemorrhoids, and a prolapsing mucosal polyp.1–4 They have a predilection for the rectum and sigmoid colon but may occur anywhere in the colorectum.1–4 The age of patients varies from 37 to 84 years, with a mean of 60 years, and occurs most commonly in women.1–4 As the name implies, these polyps are entirely benign with no reported recurrences or metastases.1–3–4

Endoscopic and Gross Findings

Endoscopically, benign fibroblastic polyps appear as single, sessile, well-circumscribed submucosal masses with overlying surface mucosal hyperplasia.3 Grossly, these polyps range in size from 0.2 to 1.5 cm with a mean, from 4 series,1–4 of 0.45 cm.

Histopathology

Histologically, benign fibroblastic polyps are characterized by a bland spindle cell proliferation within the lamina propria that separates and distorts the colonic crypt architecture1–4 (Figure 1). The epithelial surface is typically intact but may show superficial erosion.1–3–4 Hyperplastic changes are frequently present in the adjacent epithelium or intimately associated with the fibroblastic proliferation.1–4 Another common feature is a thin zone of uninvolved lamina propria, just beneath the epithelial surface, separating it from the fibroblastic proliferation.4 A zonation phenomenon may be seen with superficial spindle cells oriented parallel to the epithelial surface and a more haphazard arrangement of spindle cells deeper in the lesion.1 The deeper spindle cells are more plump and may demonstrate a concentric arrangement around vessels and crypts.2,4 Rarely, there are well-circumscribed whorls of spindle cells that resemble meningothelial-like nodules.4 Thin wisps of muscularis mucosae may extend in a radial arrangement toward the surface epithelium.1,4 There is a pushing border, and the spindle cells may be intimately associated with the muscularis mucosae but do not invade into the submucosa.1,4 The stroma contains collagen, abundant mast cells, and inflammatory cells composed predominantly of eosinophils.1,2,4 Necrosis is absent in these lesions.1,3–4

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Cytologically, the spindle cells are bland with pale, eosinophilic cytoplasm; indistinct cell borders; and oval to fusiform nuclei, with inconspicuous nucleoli (Figure 2). The cells lack pleomorphism, hyperchromasia, and significant mitotic activity.\textsuperscript{1,3,4}

**Immunohistochemical and Ultrastructural Findings**

Immunohistochemically, benign fibroblastic polyps are invariably strongly and diffusely positive for vimentin\textsuperscript{1,3,4} (Figure 3). They are negative for S100 protein (Figure 4), desmin, CD117 (c-Kit; Figure 5), epithelial membrane antigen (EMA), CD31, bcl-2, cytokeratin AE1/3, PGMI, COX-2, h-caldesmon, cyclin D1, CD21, CD23, CD35, and factor XIII.\textsuperscript{1,4} In 2 series,\textsuperscript{1,2} focal CD34 positivity was noted in 4 of 18 cases (78%), and in one series,\textsuperscript{1} focal α-smooth muscle actin positivity was noted in 2 of 14 cases (14%). However, most benign fibroblastic polyps are negative for CD34 and α-smooth muscle actin.\textsuperscript{1-4} Additionally, in one series,\textsuperscript{2} 1 of 4 cases (25%) demonstrated focal calponin positivity, and all 4 cases (100%) demonstrated fascin positivity, which may indicate follicular dendritic cell differentiation. However, other follicular dendritic cell markers (CD21, CD23, CD35, EMA, and cyclin D1) were negative.\textsuperscript{3} Ki-67 (MIB1) labeling demonstrates a proliferation index of 1% or less.\textsuperscript{3,4} Some of the immunohistochemical stains that are negative in the spindle cells are helpful in highlighting other features of benign fibroblastic polyps. The typically abundant stromal mast cells stain positively with CD117 (c-Kit; Figure 5). Stains for smooth muscle actin and desmin highlight smooth muscle fibers extending from the muscularis mucosae into the lamina propria and between crypts radially toward the epithelial surface, as well as disorganization of the muscularis mucosae\textsuperscript{1} (Figure 6).

Ultrastructurally, benign fibroblastic polyps show flat, spindle cells with long and slender cytoplasmic processes arranged within abundant collagen fibers of normal periodicity.\textsuperscript{1,4} The spindle cells demonstrate numerous intermediate filaments, scant cytoplasmic organelles, and lack basal lamina, dense bodies, fibronexus junctions, and pinocytic vesicles.\textsuperscript{1,3,4} Overall, these features support fibroblastic differentiation.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of benign fibroblastic polyps includes other spindle cell proliferations that may present as mucosal polyps within the gastrointestinal tract, including inflammatory fibroid polyps (Vanek tumor), gastrointestinal stromal tumor, schwannoma, ganglioneuroma, inflammatory clocogenic polyp, prolapsing mucosal polyp, smooth muscle tumors, and the recently described intestinal perineurioma. These can usually be separated from benign fibroblastic polyps based on a combination of morphology and immunohistochemical staining.

Inflammatory fibroid polyps (Vanek tumor) occur most commonly in the stomach but may occur in the esophagus, small intestine, and colon.\textsuperscript{6,7} Histologically, they are characterized by a proliferation of spindle and stellate cells in a loose fibromyxoid stroma that contains abundant inflammatory cells and small blood vessels.\textsuperscript{6,7} The inflammatory infiltrate is composed of an abundance of eosinophils with scattered lymphocytes, mast cells, plasma cells, and histiocytes.\textsuperscript{6,7} Another characteristic feature is a perivascular and periglandular concentric onionskin-like arrangement of the spindle cells.\textsuperscript{6,7} Immunohistochemically, the stromal cells in inflammatory fibroid polyps are typically positive for vimentin, CD34, fascin, and cyclin D1 and most are positive for calponin.\textsuperscript{6,7} Benign fibroblastic polyps lack the prominent inflammation, concentric perivascular, and periglandular arrangement of the spindle cells, and the edematous or myxoid change seen in inflammatory fibroid polyps. Although a vague, concentric, periglandular and perivascular arrangement of the spindle cells has been noted in benign fibroblastic polyps, this is typically not the predominant pattern and is considered a nonspecific histologic finding.\textsuperscript{2,5} Most benign fibroblastic polyps are negative for CD34 with rare focal positivity.\textsuperscript{1,4} They are typically cyclin D1 negative.\textsuperscript{2}

Gastrointestinal stromal tumors are most commonly found in the stomach and small intestine, but a small percentage occur in the colon.\textsuperscript{8,9} Histologically, they may be composed of either spindle or epithelioid cells.\textsuperscript{8,9} The spindle cell tumors are usually cellular with perinuclear vacuoles and occasional palisading.\textsuperscript{8,9} Tumors with epithelioid morphology have plump or round cells and may have significant pleomorphism.\textsuperscript{8,9} Mitotic activity is variable.\textsuperscript{8,9} Immunohistochemically, 76% of colonic gastrointestinal stromal tumors are positive for CD117 (c-Kit).\textsuperscript{9} Benign fibroblastic polyps are less cellular, lack atypia and mitoses, and are uniformly negative for CD117, which is the most useful feature in the differential diagnosis.

Spindle cell schwannomas typically occur in adults and are located primarily in the cecum.\textsuperscript{10} Histologically, spindle cell schwannomas are moderately to highly cellular lesions composed of spindle cells, often arranged in a trabecular pattern.\textsuperscript{10} Fibrovascular septa that contain a lymphoplasmacytic infiltrate are also common.\textsuperscript{10} These tumors are characteristically surrounded by a prominent lymphoid cuff with germinal center formation.\textsuperscript{10} Nuclear palisading, well-formed Verocay bodies, hyalinized vessels, and xanthoma cells, typically seen in soft tissue schwannomas, are not seen in the colonic variant.\textsuperscript{10} The spindle cells have slender nuclei with pointed ends and scattered cells with hyperchromasia and significant cytologic atypia.\textsuperscript{10} As with schwannomas elsewhere, colonic tumors are universally strongly and diffusely positive for S100 protein.\textsuperscript{10} Benign fibroblastic polyps are less cellular; lack the trabecular pattern, lymphoid cuff, and cytologic atypia of schwannomas; and are S100 protein negative.

True ganglioneuromas may present as solitary or multiple diminutive mucosal polyps within the gastrointestinal tract from the stomach to the colon.\textsuperscript{11} Histologically, they are composed of a mucosal spindle cell population with scattered mature ganglion cells.\textsuperscript{11} Immunohistochemically, the spindle cells are positive for S100 protein, and the ganglion cells are positive for synaptophysin and neuron-specific enolase.\textsuperscript{11} Benign fibroblastic polyps lack ganglion cells and are S100 protein negative.

As with benign fibroblastic polyps, prolapsing mucosal polyps tend to occur in the sigmoid colon.\textsuperscript{12} Histologically, prolapsing mucosal polyps demonstrate colonic crypt architectural abnormalities, including elongation, distortion, branching, and hyperplastic changes.\textsuperscript{12} The lamina propria contains a spindle cell proliferation of a fibromuscular nature.\textsuperscript{12} The muscularis mucosae is thickened and sends radial extensions into the lamina propria toward the surface epithelium.\textsuperscript{12} A mixed inflammatory infiltrate and granulation tissue are frequently present.\textsuperscript{12} The vessels demon-
Figure 1. Benign fibroblastic polyp demonstrating a bland spindle cell proliferation that expands the lamina propria with wide separation of the colonic crypts. Note the thin zone of uninvolved lamina propria just beneath the surface epithelium (hematoxylin-eosin, original magnification ×100).

Figure 2. Benign fibroblastic polyp demonstrating cells with pale, indistinct eosinophilic cytoplasm, round to spindled nuclei without cytologic atypia, and a finely collagenous stroma (hematoxylin-eosin, original magnification ×400).

Figure 3. Diffuse and strongly positive vimentin immunostain (original magnification ×100).

Figure 4. Negative S100 protein immunostain (original magnification ×100).

Figure 5. Negative CD117 (c-Kit) immunostain in benign fibroblastic polyp with abundant CD117-positive mast cells within the stroma (original magnification ×100).
strate variable changes including hyalinization, dilatation, congestion, and thrombosis. Hemorrhage, hemosiderin deposition, and surface epithelial erosions are also common features. Benign fibroblastic polyps typically do not have a fibromuscular stromal proliferation within the lamina propria. Also absent are the extensive crypt architectural abnormalities, the prominent inflammatory and granulation tissue response, and the hemorrhage and hemosiderin deposition. Benign fibroblastic polyps may have smooth muscle fibers extending into the lamina propria and rarely surface erosion, but these are not prominent features.

Leiomyomas of the muscularis mucosae of the colon and rectum have a predilection for the descending colon, sigmoid colon, and rectum. Histologically, these lesions are well demarcated and located immediately beneath the crypt epithelium and lamina propria. They are composed of intersecting fascicles of smooth muscle cells with eosinophilic cytoplasm and cigar-shaped nuclei and characteristically merge with the muscularis mucosae and appear to arise from it. Immunohistochemically, they are uniformly, diffusely, and strongly positive for desmin and smooth muscle actin. Benign fibroblastic polyps involve the lamina propria, distort the crypt architecture, do not have a fascicular pattern of growth, are negative for desmin, and are only rarely positive for smooth muscle actin.

Intestinal perineuriomas were first described by Hornick and Fletcher in 2005. Intestinal perineuriomas share many clinical features with benign fibroblastic polyps. They are typically discovered on routine screening colonoscopy as small sessile polyps in asymptomatic patients and have a predilection for the sigmoid colon and rectum. They have a variable predominance in women and occur most commonly in the fifth decade of life, with an age range of 35 to 84 years. Intestinal perineuriomas also share many common histologic features with benign fibroblastic polyps. Intestinal perineuriomas are composed of an intramucosal, bland, spindle cell proliferation within a fine collagenous stroma. These lesions tend to entrap the crypt epithelium and have irregular borders with adjacent uninvolved lamina propria. Occasionally the spindle cells have a focal periglandular whorled pattern. The surface epithelium is intact without ulceration or erosion. Hyperplastic change is commonly evident within the lesions and in the adjacent epithelium. The muscularis mucosae may be focally disorganized and have smooth muscle bundles radiating toward the surface epithelium. Cytologically, the cells have indistinct, pale, eosinophilic cytoplasm and oval to spindled nuclei. Pleomorphism, cytologic atypia, and mitotic figures are not seen in these lesions. Immunohistochemically, intestinal perineuriomas are typically epithelial membrane antigen positive. The staining for EMA is generally weak and must be assessed at high magnification. These lesions are also positive for other perineurial markers including claudin-1, GLUT1, and collagen type IV. Some cases may show CD34 positivity. Intestinal perineuriomas are negative for S100 protein, smooth muscle actin, desmin, caldesmon, CD117 (c-Kit), pancytokeratin, glial fibrillary acidic protein, and neurofilament protein. Ultrastructurally, intestinal perineuriomas are composed of spindle cells with sparse organelles and thin cytoplasmic processes within a collagenous background. Necrotic vesicles, basal lamina, and primitive cell junctions are also identified. These findings are typical for perineurial cells. This is the most challenging lesion to differentiate from benign fibroblastic polyps, and some have concluded that intestinal perineurioma and benign fibroblastic polyps may be the same entity. These 2 lesions have remarkably overlapping clinical and histologic features.

The major distinguishing feature is the lack of EMA positivity in most reported cases of benign fibroblastic polyps. However, Zamecnik and Chlumská reevaluated their original 4 cases of benign fibroblastic polyps with an additional identified case, and using a higher antibody concentration found EMA to be diffusely positive in 3 of 5 cases (60%), 4 of which (80%) were originally reported as negative. Additionally, claudin-1 was focally positive in 4 of 5 cases (80%), and GLUT1 was strongly positive in all 5 cases (100%). When confronted with a lesion resembling a benign fibroblastic polyp or intestinal perineurioma, an immunohistochemical panel that uses at least 2 markers of perineurial differentiation (EMA, claudin-1, GLUT1, or type IV collagen) and the use of a high antibody concentration, a prolonged incubation time, and/or an extended method of antigen retrieval for EMA immunostaining, is recommended.

CONCLUSIONS

Benign fibroblastic polyps are a rare cause of mucosal polyps in the colon; however, increased awareness of this entity, among pathologists, will likely lead to increased recognition and diagnosis. Most commonly, they are discovered as solitary mucosal polyps in asymptomatic patients undergoing routine screening colonoscopy. Most occur in the sigmoid colon and rectum. They occur primarily in women in the sixth decade of life. Microscopically, they are characterized by a bland spindle cell proliferation within the lamina propria that displaces and entraps the crypt epithelium. Additional features include a thin zone of uninvolved lamina propria separating the lesion from the surface epithelium and the frequent occurrence of hyperplastic epithelium both adjacent to and within the lesion. Benign fibroblastic polyps stain diffusely and strongly positive with vimentin and are also positive for fascin. They are typically negative for S100 protein, epithelial membrane antigen, desmin, smooth muscle actin (rarely focally positive), CD117 (c-Kit), and CD34 (rarely focally positive). The differential diagnosis includes other spindle cell lesions that cause colonic mucosal polyps including inflammatory fibroid polyps (Vanek tumor), gastrointestinal stromal tumor, schwannoma, ganglioneuroma, inflammatory cloacogenic polyp, prolapsing mucosal polyp, leiomyoma, and the recently described intestinal perineurioma. Most of these entities can be readily distinguished from benign fibroblastic polyps with a combination of morphology and immunohistochemistry. The most difficult differential diagnosis is with intestinal perineuriomas because these lesions have essentially the same clinical and histologic features as benign fibroblastic polyps. In

Figure 6. Negative smooth muscle actin immunostain in benign fibroblastic polyp with positive staining of the disorganized muscularis mucosae and bundles of smooth muscle radiating toward the surface epithelium (original magnification ×100).
fact, intestinal perineuriomas and benign fibroblastic polyps may represent the same entity. For now, immunohistochemical staining employing at least 2 perineurial markers, such as GLUT1, claudin-1, type IV collagen, or EMA, which are typically positive in intestinal perineuriomas, should allow this distinction to be made. Epithelial membrane antigen immunostaining should include high antibody concentration, prolonged incubation time, and/or extended antigen retrieval to increase yield. Benign fibroblastic polyps are biologically innocuous because, to our knowledge, there have been no reported recurrences or metastases.

References