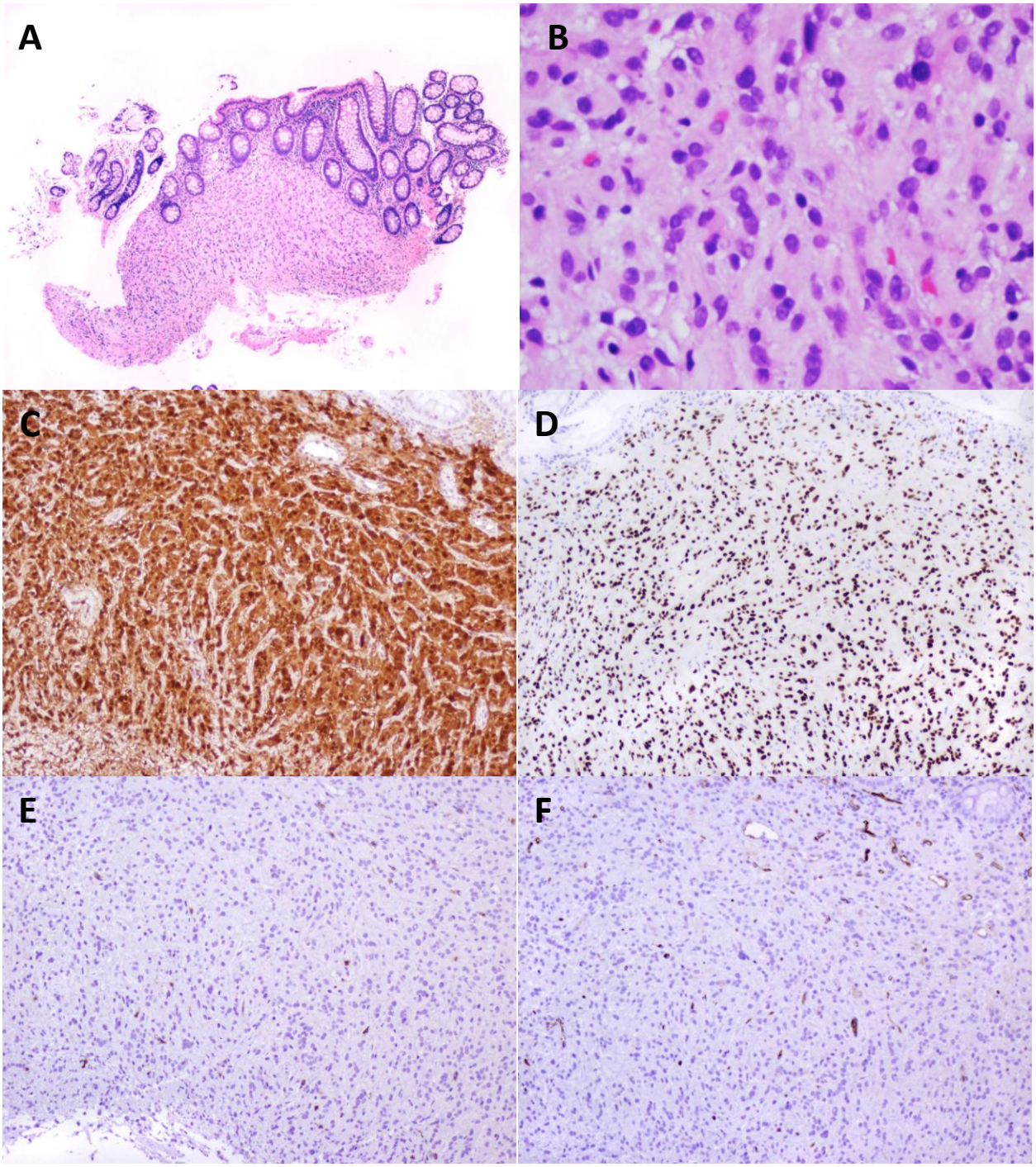
A 25 year old male with no significant past medical history presented with abdominal pain and rectal bleeding, a colonoscopy was recommended. Upon endoscopic examination, a polyp was noted in the transverse colon; no other abnormalities were identified. The polyp was biopsied and sent for histologic examination. Representative H&E, S100, SOX10, CD34 and CD117 images for review:



A) H&E 4x, B) H&E 40x, C) S100 10x, D) SOX10 10x, E) CD117 10x, F) CD34 10x

What is the diagnosis?

A) Granular cell tumor
B) Neurofibroma
C) GIST
D) Benign epithelioid nerve sheath tumor
E) Melanoma

ANSWER AND DISCUSSION ON NEXT PAGE

Answer and discussion:

Benign epithelioid nerve sheath tumor (choice D) is the correct answer. Histologic sections show the colonic lamina propria to be expanded by a proliferation of bland, epithelioid cells with round-to-oval nuclei, frequent intranuclear pseudoinclusions and a moderate amount of eosinophilic cytoplasm. Mitotic activity is not appreciated. The growth pattern of this proliferation appears slightly whorled. While the proliferation appears to push glands aside, destruction or invasion of the epithelium is not seen; the glanular epithelium overlying and adjacent to the lesion appears intact with minimal reactive changes. The lesion's cells were found to be immunoreactive for antibodies against S100, SOX 10 and CD56, while pancytokeratin, CD117 and CD34 were negative with focal SMA and desmin staining present (possibly representing entrapped muscularis mucosae), and Ki67 stain showed a proliferation index of less than 2%.

Benign epithelioid nerve sheath tumors (BEPNSTs) have been reported to involve the mucosa of the colon and bladder as well as the skin and subcutaneous tissues. They generally present in the colon as polyps measuring < 1cm and are found on routine colonoscopy procedures or incidentally during work-up of unrelated complaints and follow a benign clinical course. BEPNSTs of the colon are centered in the lamina propria, often with superficial extension into the submucosal tissues and are composed of epithelioid cells, often with a component of admixed spindle cells, arranged in nests and whorls. The lesional cells display round-to-oval nuclei with prominent intranuclear pseudoinclusions and eosinophilic fibrillary cytoplasm. Mitotic figures are generally not seen. It has been debated whether these small epithelioid lesions represent variations of more traditional schwannomas or neuromas, but what is agreed upon is that they lack the define characteristics of either lesion (Antoni A or B areas, intralesional neuroaxons or association with peripheral nerves). However attempts to classify these lesions have only recently begun. These lesions do demonstrate the immunohistochemical features of neural-type differentiation and uniformly express S100 and CD57, with variable staining for CD34. They are negative for CD117, SM31, calretinin, melanoma markers and epithelial markers. Staining with CD56 and SOX10 has yet to be reported in the literature. The positivity for these markers in this case further supports neural-type differentiation. A lesion which perhaps represents a close cousin to BEPNST is the Mucosal Schwann Cell Hamartoma (MSCH) which was well described by Drs. J. Hornick and J. Gibson (AJSP 2009). MSCHs will stain similarly to BEPNST with strong, diffuse S100 positivity and will likewise be negative for EMA, CD34, CD117 and SMA, but may perhaps differ with a minority of cases showing neurofilament protein positivity. MSCH will also be centered in the lamina propria, however MSCHs have been described as surrounding and entrapping colonic crypts rather than pushing them aside; they feature spindled rather than epithelioid cells; and finally MSCH nuclei are spindled and tapered without prominent intranuclear inclusions.

Granular cell tumors are also benign epithelioid tumors thought to be derived from or differentiated toward Schwann cells that may occur throughout the mucosa of the GI tract. The lesional cells appear as nests or sheets of polygonal cells with abundant granular eosinophilic cytoplasm and small, uniform nuclei. These cells are diffusely positive for S100, CD57, calretinin and myelin basic protein; the cytoplasmic granules represent lysosomes that are PAS positive with diastase-resistance. The features that distinguish granular cell tumors from BEPNSTs are the small, non-vacuolated nuclei, the granularity of the cytoplasm and the immunoreactivity with myelin basic protein.

Neurofibromas are another S100-positive neurally differentiated process that may present as polyps involving the colonic lamina propria. Although neurofibromas can present incidentally as isolated polyps in patients without a significant medical history, it is very rare that they involve the GI tract outside the

setting of neurofibromatosis type 1. These lesions represent hyperplasia of the peripheral neuronal cells and may occur in the submucosa, muscularis propria or serosa and may extend into the lamina propria. Lesional cells are immunoreactive for S100 and may show reactivity for CD34 and Factor 13a. As opposed to our case, the lesional cells in neurofibroma are more spindled and are often admixed with collagen fibrils and mast cells.

Gastrointestinal stromal tumors may occur in any organ along the length of the tubular gastrointestinal tract and may be spindled- or-epithelioid in appearance. They are most often centered in the muscularis propria, but can be sampled in mucosal biopsies. They are an important entity to consider and identify as they have a targeted therapy and may behave in a malignant manner. GISTs may display palisading, collagen fibrils and perinuclear cytoplasmic vacuoles. The vast majority of GISTs harbor kit mutations and will stain for CD117. DOG1 is also a useful marker for GIST, but may also be positive in a subset of gastric adenocarcinomas (an important pitfall if considering this differential in the stomach or esophagus). Additionally, approximately 70% of GIST will be immunoreactive for CD34, and a minority of epithelioid GISTs may stain with Melan A. GISTs will be negative for S100, SOX10 and cytokeratin.

Malignant melanoma is known to present as polypoid masses involving the GI tract, most frequently the small bowel. While the lesional cells may appear epithelioid, they will also display marked cytologic atypia with nuclear pleomorphism, prominent nucleoli and frequent mitotic figures; findings in stark contrast to the bland, uniform and mitotically inactive BEPNSTs. Immunohistochemical stains HMB45 and Melan-A can be positive in addition to S100 and SOX10 to aid in this differential.

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Case contributed by:

Felicia D. Allard, MD
Clinical Fellow
&

Stacey E. Mills, MD
Professor of Pathology
Director of Surgical Pathology and Cytopathology

Department of Pathology
University of Virginia
Charlottesville, VA