Primary neurogenic gastrointestinal polyps are encountered relatively frequently in routine pathology practice. They encompass a variety of neoplastic entities with clinical, morphologic, and molecular features that reflect the diversity of neural elements within the gastrointestinal system. Although most are benign and encountered incidentally, accurate diagnosis may have important clinical implications because of the associations of certain neurogenic polyps with familial syndromes or other conditions. We review the pathology of these polyps with an emphasis on the diagnostic challenges that they pose and on newly described subtypes.

Although the great majority of endoscopically resected gastrointestinal (GI) polyps are of epithelial derivation, a variety of lesions derived from neural components of the GI tract, or neurogenic polyps, may be encountered in pathology practice. The third most common group of GI mesenchymal tumors after GI stromal tumors (GISTs) and leiomyomas,1 neurogenic polyps encompass a variety of clinically and pathologically distinct entities including schwannoma, granular cell tumor, perineurioma, neurofibroma, ganglioneuroma, and gangliocytic paraganglioma. The differential diagnostic challenges posed by these lesions can have important clinical implications, including syndromic associations that might otherwise go unrecognized. In this review we summarize the distinctive clinical, histologic, and immunohistochemical characteristics of each of these polyps.

SCHWANNOMA AND SCHWANN CELL HAMARTOMA

Clinical

Schwannomas are benign nerve sheath tumors that account for 2% to 6% of GI mesenchymal tumors.2 Their incidence is similar between men and women, although some studies have identified a slight female predominance.2,3 The peak incidence is in the third through sixth decades.

Clinical presentations depend on tumor location and size, ranging from incidental discovery to prominent symptoms such as dysphagia or rectal bleeding.

Conventional schwannomas, or neurilemmomas, average 5 cm in size, with a broad range of 0.1 to 14 cm.2 Although they may be encountered throughout the GI tract, approximately 70% occur in the stomach.1,2 They usually are located within the submucosa or muscularis propria and may present at endoscopy as bulging masses, sometimes with ulceration of the overlying mucosa. Cut section reveals a well-circumscribed but unencapsulated firm mass with a tan-white, often myxoid surface.

Schwannomas may occur in association with 2 syndromes, schwannomatosis and Carney complex. In schwannomatosis, germline mutations of the tumor suppressor SMARCB1/INI1 at position 22q11.23 are often present with second-hit mutations in SMARCB1/INI1 and additional somatic mutations in the NF2 gene at position 22q12.2, which result in a truncated Merlin protein that can no longer function in cellular growth arrest.3 NF2 is mutated in sporadic schwannomas as well as in those occurring in patients with neurofibromatosis 2 who develop bilateral acoustic schwannomas. Nonetheless, GI schwannomas are rarely associated with NF2 mutations,4 and, to the authors’ best knowledge, have not been described in association with schwannomatosis. In Carney complex, patients develop upper GI schwannomas or psammomatous melanotic schwannomas in addition to lentigines, nevi, myxomas, pituitary adenomas, large cell calcifying Sertoli cell tumors, and follicular thyroid lesions.5

Microscopic

Intramural GI schwannomas often feature a peripheral lymphoid cuff that is visible at low magnification (Figure 1, A). The tumor cells are usually spindleled and arranged in Antoni A (ie, cellular areas with palisading Verocay bodies) and Antoni B (ie, myxoid hypocellular) areas, albeit sometimes only focally and indistinctly.4 Mitoses are rare and the nuclei are usually cytologically bland with tapered ends; however, nuclear pleomorphism and atypia may occur as a result of degenerative change, the term ancient schwannoma being used when these changes are prominent.
The main differential diagnosis of schwannoma includes GIST and neurofibroma. In addition to the peripheral lymphoid cuff, schwannomas are distinguished from GISTs by CD56 positivity; diffuse, strong expression of S-100; negative staining for KIT; and absence of subnuclear vacuoles typical of GISTs. Additionally, the majority of schwannomas are positive for calretinin, whereas most neurofibromas are negative for calretinin and show weak, patchy S-100 staining. An increased mitotic rate, albeit rare, should raise concern for malignant transformation.

Variant histologic patterns and subtypes of schwannomas have been described, some of which mimic other tumors or have unique clinical implications. Epithelioid intramural schwannomas have been reported but are extremely rare. Tozbikian et al reported signet ring features in a submucosal gastric schwannoma with myxoid stroma. Schwannomas variously termed microcystic, reticular, or pseudoglandular have been described throughout the GI tract but seem to have a predilection for the colon, where they present as polyps. Approximately 12 cases of this variant have been reported to date, their descriptions including intermixed or discontinuous epithelioid and signet ring components (Figure 1, B) and an inconspicuous peripheral lymphoid cuff. Microcystic schwannomas are positive for Alcian blue at pH 2.5 because of acid mucin content and may express CD34. The differential diagnosis from adenocarcinoma is based on their distinctive features, including circumscription, bland cytology, lack of desmoplasia, diffuse and strong expression of S-100, and negative cytokeratin staining.

Mucosal Schwann cell proliferations termed Schwann cell hamartoma or benign epithelioid nerve sheath tumor have a strong predilection for the colon, where they present incidentally as small polyps (<1 cm). Microscopically, they are limited mostly to the lamina propria. Unlike conventional schwannomas, they are uncircumscribed, infiltrate around and between individual crypts, and lack cellular atypia, a lymphoid cuff, and prominent Verocay bodies (Figure 1, C). Intranuclear vacuoles and infiltration of the superficial submucosa have been described as distinctive features.

Psammomatous melanotic schwannoma may present rarely as a colorectal polyp comprising epithelioid cells with psammoma bodies and melanin pigment. Despite the combination of melanin pigmentation and expression of HMB-45 and S-100, it can be distinguished from melanoma based on the absence of prominent nuclei, small nuclear size, and lack of desmoplastic response.
Malignant transformation of schwannomas is extremely rare, with only one case series reported, and has not been described to date in the GI tract to our knowledge. It may take the form of malignant peripheral nerve sheath tumor, including its epithelioid variants, or of angiosarcoma, microscopic clues including epithelioid change and increased mitoses.

**GRANULAR CELL TUMOR**

**Clinical**

Granular cell tumor (GCT) is currently thought to be of Schwann cell origin. It occurs equally in males and females, mostly in adults. The most common locations are the tongue and skin but any organ may be involved. In the GI tract, most GCTs occur in the esophagus, with more than 300 cases reported, followed by the right colon, with more than 100 colorectal cases reported. Presenting symptoms depend on location and size, and include dysphagia, pain, heartburn, or hematochezia, but some tumors are found incidentally. Endoscopically, they usually present as small sessile, or occasionally pedunculated, nodules covered by intact mucosa.

Multiple non-GI GCTs have been described in patients with LEOPARD syndrome and Noonan syndrome, both autosomal-dominantly transmitted conditions characterized by mutation in the protein tyrosine phosphatase, non-receptor type 11 gene (PTPN11). Multiple, mostly upper-tract GI GCTs have been reported in patients with neurofibromatosis 1.

**Microscopic**

Gastrointestinal GCTs arise most frequently within the lamina propria of the esophagus or the submucosa of the colon. The tumor border may be infiltrative or circumscribed. The tumor cells are polygonal or fusiform and arranged in sheets or cords, often with interspersed bands of dense collagen. The cytoplasm is abundant, eosinophilic, and, as the name suggests, granular, reflecting the presence of abundant lysosomes, and the nuclei are typically small, dark, and monomorphous (Figure 2). Granular cell tumors express S-100, CD56, calretinin, neuron-specific enolase, vimentin, CD68, periodic acid–Schiff with diastase, α1-antitrypsin, and α1-antichymotrypsin. They show variable expression of KIT and cytokeratin, negative to focal expression of glial acidic fibrillary protein, and negative staining for neurofilament.

The combination of infiltrative pattern, abundant cytoplasm, and S-100 expression in GCT may mimic melanoma, but the granular cytoplasm, small nuclei, and lack of prominent nuclei, as well as the lack of HMB45 and Melan-A expression, in GCT are distinguishing features. A diagnostic problem associated with esophageal GCT is posed by pseudop epitheliomatosus hyperplasia and reactive atypia of the overlying squamous epithelium, which can closely mimic squamous cell carcinoma (Figure 2, B). As a rule of thumb, carcinoma should be diagnosed only when the atypical epithelium extends beyond the bounds of the GCT. In the rectum, GCT may cause prolapse-related changes such as atypia of the crypt epithelium, which can simulate an adenoma.

Although the vast majority of GI GCTs are benign, malignant counterparts rarely occur in the esophagus and stomach. Criteria for malignancy in soft tissue GCTs include size larger than 5 cm, cellularity, tumor necrosis, tumor cell spindling, nuclear pleomorphism, increased nuclear and nucleolar size, and mitotic index above 2 per 50 high-power fields; however, the reliability of these criteria has not been validated in cases involving the GI tract.

**NEUROFIBROMA**

**Clinical**

Neurofibromas are tumors of nonmyelinating Schwann and perineurial cells. They occur either sporadically or in a syndromic setting including neurofibromatosis 1/von Recklinghausen disease, multiple endocrine neoplasia type IIb, or intestinal neurofibromatosis. Sporadic neurofibromas occur in middle-aged adults, equally in men and women, arising mostly in the small or large intestine and accounting for approximately 1 in 907 colon polyps, whereas upper GI tract involvement is more common in syndromic settings.

Both GI and non-GI neurofibromas occur as localized, diffuse, or plexiform types. Localized neurofibromas, the most common, account for 90% of all (GI and non-GI) neurofibromas. Diffuse neurofibromas are characterized by an infiltrative growth pattern with frequent transmural involvement of the enteric wall. Approximately 10% of all diffuse neurofibromas (GI and non-GI) are associated with neurofibromatosis 1. Plexiform neurofibromas, characterized by a “bag of worms” configuration, are closely
associated with neurofibromatosis 1, and are rarely encountered in the GI tract.30

Patients with neurofibromatosis 1 carry an autosomal-dominantly inherited mutation in the NF1 gene at position 17q11.2, causing a loss of function of the tumor suppressor gene.7,36–38 The myxoid matrix often stains with Alcian blue.39

Another predisposing syndrome is multiple endocrine neoplasia type IIIb, in which patients develop GI neurofibromas characteristically in association with neurofibromatosis 1 and multiple endocrine neoplasia type IIIb; NF1, neurofibromatosis 1; NF2, neurofibromatosis 2; NSE, neuron-specific enolase.

Abbreviations: EMA, epithelial membrane antigen; GFAP, glial fibrillary acidic protein; GLUT1, glucose transporter 1; MEN IIb, multiple endocrine neoplasia type IIb; NF1, neurofibromatosis 1; NF2, neurofibromatosis 2; NSE, neuron-specific enolase.

**Immunohistochemical Properties and Syndromic Associations of Neurogenic Polyps**

<table>
<thead>
<tr>
<th>Immunohistochemical propertiesa</th>
<th>Schwannoma</th>
<th>Granular Cell Tumor</th>
<th>Neurofibroma</th>
<th>Ganglioneuroma</th>
<th>Perineuroma</th>
<th>Gangliocytic Paraganglioma</th>
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<td>S-100</td>
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<td>CD56</td>
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<td>NSE</td>
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<td>Neurofilament</td>
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<td>GFAP</td>
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<td>Synaptophysin</td>
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<td>CD34</td>
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<td>Focal +</td>
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<td>Calretinin</td>
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Syndromic associationsb

- NF1
- NF2
- MEN IIb
- PTEN syndromes
- Carney complex
- Noonan syndrome
- LEOPARD syndrome
- Juvenile polyposis
- Tuberous sclerosis

Abbreviations: EMA, epithelial membrane antigen; GFAP, glial fibrillary acidic protein; GLUT1, glucose transporter 1; MEN IIb, multiple endocrine neoplasia type IIb; NF1, neurofibromatosis 1; NF2, neurofibromatosis 2; NSE, neuron-specific enolase.

a For immunohistochemical properties: –, negative; +, weakly positive; ++, moderately positive; ++++, strongly positive.

b For syndromic associations: +, present.

GANGLIONEUROMA

**Clinical**

Ganglioneuromas are benign hamartomatous polyps that comprise ganglion cells, peripheral nerve, and supporting cell elements. They may occur singly or multiply anywhere in the GI tract, but more than half arise in the colon.35

Isolated polypoid ganglioneuromas are uncommon sporadic lesions. They occur equally in males and females, and can occur at any age but show a peak between 40 and 60 years.35 Patients may be asymptomatic or may present with rectal bleeding, pain, or symptoms of irritable bowel. At colonoscopy, the polyps are usually smaller than 2 cm and may be sessile or pedunculated.40

Diffuse ganglioneuromatosis refers to masslike intramural or transmural expansions of the myenteric plexus and nerve tracts by neural, ganglionic, and stromal elements and is associated with neurofibromatosis 1 and multiple endocrine neoplasia type IIb.
neoplasia type IIb. Polypoid or diffuse mucosal ganglioneuromatosis is associated with these syndromes as well as the PTEN hamartomatous polyposis syndromes Cowden disease and Bannayan-Ruvalcaba-Riley syndrome. 40 Patients with Cowden disease are at an increased risk for development of follicular carcinomas of the thyroid and ductal carcinoma of the breast.

Microscopic

Ganglioneuromas typically occupy the lamina propria and may extend into the submucosa. The lamina propria is expanded by a proliferation of S-100–positive spindle cells with wavy or comma-shaped nuclei intimately admixed with aggregates of ganglion cells. As in neurofibromas, mast cells may be scattered throughout. The presence of ganglion cells, readily confirmed by staining for neuron-specific enolase and neurofilament, sets ganglioneuromas apart from other neurogenic spindle cell lesions such as neurofibroma.

GANGLIOCYTIC PARAGANGLIOMA

Clinical

Gangliocytic paraganglioma accounts for approximately 9% of all duodenal endocrine tumors. Its has a slight male predominance and is diagnosed from the third to ninth decade with a peak in the sixth decade. About 90% of tumors arise near the ampulla of Vater; however, other sites may be involved throughout the upper to mid GI tract as well as extraintestinal sites such as the lower spinal cord and respiratory tract. They range in size from 0.55 to 10 cm. Almost half of patients present with GI bleeding or pain, and endoscopy typically reveals a submucosal-based mass.
with mucosal ulceration. Neurofibromatosis 1 patients are at increased risk of developing this tumor.

**Microscopic**

The tumor consists of 3 intimately admixed cell types: spindle cells, ganglion cells, and epithelioid cells. The spindle cells are often the most prominent component, with ganglion-like cells embedded throughout as in ganglioneuma (Figure 5, A). The ganglion-like cells are positive for synaptophysin and neuron-specific enolase, but in some tumors express somatostatin and pancreatic polypeptide. The epithelioid cells are arranged in ribbons, nests, pseudoglandular structures, or trabeculae (Figure 5, B). They have eosinophilic to amphiphilic cytoplasm and often contain secretory granules that express somatostatin or lysozyme. The cytoplasm is usually positive for neuron-specific enolase, synaptophysin, pancreatic polypeptide, CD56, glial acidic fibrillary protein, somatostatin, and chromogranin A; about half express cytokeratin, and 20% express serotonin. Although generally submucosal based, a majority of tumors extend into the muscularis propria and in rare cases extend transmurally into the perienteric connective tissue or even metastasize to regional lymph nodes. The differential diagnosis includes pheochromocytoma, well-differentiated neuroendocrine tumor, and ganglionneuma. Adequate sampling following resection will permit this distinction, but biopsy diagnosis may be challenging.

**HYBRID NEUROGENIC POLYPS**

Nerve sheath–derived polyps with combined features have been described. The most frequently documented is hybrid schwannoma/perineuroma, followed by rarer cases of neurofibroma/perineuroma and schwannoma/neurofibroma. To date, these hybrid polyps have not been associated with known syndromes and have followed a benign course.

Hybrid schwannoma/perineuroma is characterized microscopically by a plexiform architecture and storiform growth pattern with collagenous stroma typical of perineuroma combined with nodular areas of Schwann cell differentiation and corresponding cytologic features. The latter component may predominate, and some tumors exhibit degenerative atypia typical of conventional schwannomas. Immunohistochemically, 2 distinctive but intimately admixed groups coexist: perineurial cells expressing epithelial membrane antigen, claudin-1, and GLUT1, and Schwann-like cells expressing S-100. Hybrid neurofibroma/perineuroma may feature whorlike patterns characteristic of perineuroma that express perineurial markers along with a neurofibroma component that stains for S-100. Hybrid schwannoma/neurofibromas exhibit a plexiform architecture with nodular areas of Schwannian differentiation.

**CONCLUSIONS**

Neurogenic polyps of the GI tract, although less frequently encountered than other types of polyps, encompass a diverse range of interesting and diagnostically challenging entities, some of which may provide the clue to an underlying syndromic condition. Attentiveness to the histologic details and judicious use of immunohistochemical stains, summarized in the Table, in combination with relevant clinical and endoscopic data will generally permit their accurate classification and appreciation of their clinical significance.

**References**


