other genes that function in these pathways (*NF1*, *BRAF*, *HRAS*, or *NRAS*). However, more common are mutations in genes encoding components of the mitochondrial succinate dehydrogenase complex (*SDHA, SDHB, SDHC, SDHD*). These mutations, which cause loss of SDH function, are often inherited in the germline and confer an increased risk for GIST and paraganglioma (*Carney-Stratakis syndrome*, not to be confused with Carney triad); with the second copy of the affected gene being either mutated or lost in the tumor. The mechanisms by which SDH mutations lead to GIST are unclear; one hypothesis is that the accumulation of succinate leads to dysregulation of hypoxia inducible factor-1α (HIF-1α), which results in increased transcription of the vascular endothelial growth factor (*VEGF*) and insulin-like growth factor-1 (*IGF1R*) genes.

Mutation of KIT or PDGFRA is an early event in sporadic GISTs and is detectable in lesions as small as 3 mm. Therefore, *KIT* or *PDGFRA* mutations alone are insufficient for tumorigenesis. Changes associated with progression to overt GIST are not well-defined, but loss or partial deletion of chromosomes 14 and 22 is common and losses and gains at other chromosomes also occur. In particular, deletion of 9p results in loss of the cell cycle regulator *CDKN2A*, a tumor suppressor that is involved in many cancers. In addition to potentially being related to progression, increased numbers of chromosomal alterations correlate with poor prognosis.

MORPHOLOGY

Primary gastric GISTs can be quite large, as much as 30 cm in diameter. They usually form a solitary, well-circumscribed, fleshy mass (Fig. 17-21*A*) covered by ulcerated or intact mucosa (Fig. 17-21*B*), but can also project outward toward the serosa. The cut surface shows a whorled appearance. Metastases may take the form of multiple serosal nodules throughout the peritoneal cavity or as one or more nodules in the liver; spread outside of the abdomen is uncommon, but can occur. GISTs composed of thin elongated cells are classified as **spindle cell type** (Fig. 17-21*C*), whereas tumors dominated by epithelial-appearing cells are termed **epithelioid type**; mixtures of the two patterns also occur. The most useful diagnostic marker is KIT, which is detectable in Cajal cells and 95% of gastric GISTs by immunohistochemical stains.

Clinical Features. Symptoms of GISTs at presentation may be related to mass effects. Mucosal ulceration can cause blood loss, and approximately half of individuals with GIST present with anemia or related symptoms. GISTs may also be discovered as an incidental finding during radiologic imaging, endoscopy, or abdominal surgery performed for other reasons. Complete surgical resection is the primary treatment for localized gastric GIST. The prognosis correlates with tumor size, mitotic index, and location, with gastric GISTs being less aggressive than those arising in the small intestine. Recurrence or metastasis is rare for gastric GISTs smaller than 5 cm but common for mitotically active tumors larger than 10 cm. Many tumors fall into an intermediate category where the malignant potential of the lesion cannot be predicted with certainty on the basis of histology alone.

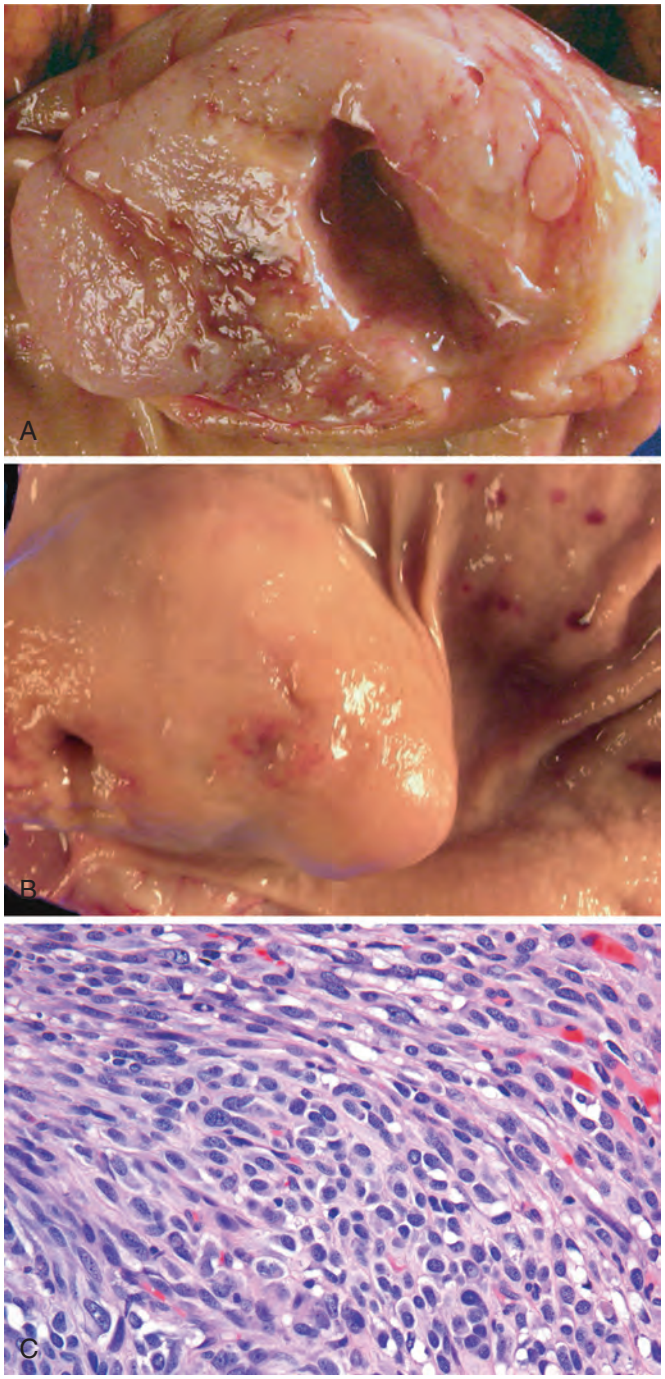

Figure 17-21 GI stromal tumor. **A,** On cross-section a whorled texture is evident within the white, fleshy tumor. **B,** The mass is covered by intact mucosa. **C,** Histologically the tumor is primarily composed of bundles, or fascicles, of spindle-shaped tumor cells. (Courtesy Dr. Christopher Weber, The University of Chicago, Chicago, Ill.)

The molecular phenotype is an important consideration in the treatment of patients with unresectable, recurrent, or metastatic GISTs. Those with mutations in *KIT* or *PDGFRA* often respond to the tyrosine kinase inhibitor imatinib. In contrast, tumors without these mutations are generally resistant. Further, specific *KIT* or *PDGFRA* mutations are associated with different drug sensitivities. In treated patients, development of imatinib-resistance is common.